

Is unrecognized anaphylaxis a cause of sudden unexpected death?

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Summary

Background Serum tryptase levels reflect mast cell activation and correlate with anaphylactic reactions. Elevated post-mortem serum tryptase levels have been found in witnessed fatal anaphylaxis.

Objective This study was designed to examine whether or not unwitnessed anaphylaxis may be a hitherto unrecognized cause of sudden unexplained death.

Methods Mast cell tryptase was measured by immunoassay in 68 post-mortem sera remaining from a previous study which reported elevated venom-specific IgE antibodies in 22 (23%) of 94 victims of sudden unexpected death. Autopsies were performed in all cases. The cause of death was independently reported by pathologists unfamiliar with the nature of this study.

Results Serum tryptase levels were elevated (>10 ng/mL) in nine of 68 cases. The levels could not be predicted from the clinical circumstances surrounding death. Sera from four individuals contained both elevated tryptase and previously reported elevated venom-specific IgE.

Conclusions We conclude that mast cell activation may accompany up to 13% of sudden unexpected deaths in adults. Measurement of both tryptase and specific IgE antibody levels in post-mortem sera from persons experiencing sudden, unexpected death may identify a small subset of cases due to clinically unrecognized fatal anaphylaxis, including those due to insect stings.

Keywords: fatal anaphylaxis, death, mast cell tryptase, insect sting allergy, venom specific IgE

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Introduction

Anaphylaxis is the clinical expression of a systemic immediate hypersensitivity reaction, mediated by the release of mediators of inflammation from mast cells and possibly basophils [1,2]. In sensitized individuals these reactions can be initiated by the interaction of multivalent antigens with specific IgE antibodies bound to high affinity receptors on mast cells and basophils. In other cases, anaphylaxis can result from direct non-

immunological activation of these cell types or can be idiopathic [3]. Tryptase is a neutral protease released from mast cell secretory granules when these cells degranulate [4]. Serum tryptase levels rise after non-fatal anaphylaxis induced by a bee sting, reach a peak from 30 min to 1 h after the sting, and then decline with a half-life of about 2 h [5–7]. Tryptase levels in sera reflect mast cell activation and correlate closely with the clinical severity of the anaphylactic reaction, as measured by decline in mean arterial pressure [7].

Elevated mast cell tryptase levels (range = 12–150 000 ng/mL) have been observed in serum samples obtained

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pre-mortem or up to 24 h post-mortem from 17 of 19 cases of witnessed fatal anaphylaxis due to hymenoptera stings, foods, or the administration of diagnostic or therapeutic agents, but not in a total of 57 sera drawn at various intervals (range 1–15 h) post-mortem from six persons dying of causes unrelated to anaphylaxis [8] demonstrating that pre-mortem mast cell activation can be precisely determined post-mortem. It has been previously speculated that anaphylaxis may be an unrecognized cause of death in persons dying unexpectedly [9]. In 1988 we reported a series of 94 cases of sudden unexplained deaths, and there was a 23% prevalence of significantly elevated hymenoptera venom-specific IgE antibodies in these persons [9]. Our current study shows that tryptase levels are elevated in 13% of the previously collected sera, suggesting anaphylaxis as a cause of death in these decedants.

Materials and methods

Sixty-eight post-mortem sera, all that remained from a previous study of persons who had died unexpectedly from medical unexplained causes [9], were utilized in this project. These sera had been collected between late May and early November of 1982, during the insect sting season in northeast Ohio, from a series of 94 subjects, aged 15–65 who had died unexpectedly and were brought to the office of the Cuyahoga County Coroner. Clinical data were skimpy; no detailed medical record or past history for any of these persons was available. No medical interviews of family members were possible; indeed, the study was conducted in a blinded fashion, so that only the ages, sex, immediate clinical situation at the time of death and the gross autopsy findings were known. Autopsies were the nature of our study; sera were taken from post-mortem blood specimens were separated for toxicological studies. Known insect sting cases were excluded from study, i.e. one person who witnessed by a co-worker to have had a yellow jacket sting and then

collapse and die, was excluded from the study. Post-mortem intervals ranged from several hours to an extreme of 48 h before serum was collected. Clinical synopsis and pathological diagnoses were collected by one of the authors (H.J.S.).

These sera had been studied for the presence of venom-specific IgE antibodies with a mini-RAST technique [10]. Briefly, positive and negative control sera, or test sera were reacted with solid-phase allergens prepared by linking honeybee, wasp, yellow jacket, yellow hornet, or white-faced hornet venoms to cyanogen bromide-activated micro crystalline cellulose particles. After incubation, the venom-cellulose IgE antibody complex was washed, incubated with radiolabelled anti-human IgE, washed and counted in a gamma spectrometer. Results were expressed as percentage of the radioactive binding produced by serum from a non-allergic individual. Values greater than 300% of negative control were considered elevated, while values between 200 and 300% of control were considered somewhat elevated; values below 200% control were considered to be within normal limits.

Tryptase levels were measured by a radioimmunosorbent assay as previously described [8]. Levels equal to or greater than 10 ng/mL were considered to reflect substantial mast cell activation; levels of 5–9.9 ng/mL were considered to reflect modest mast cell activation; and levels <5 ng/mL were considered to indicate that mast cell activation had not occurred near the time of death [8]. The lower limit of sensitivity for the assay was 1 ng/mL.

'We originally chose to measure venom-specific IgE antibodies because in many cases of fatal insect sting anaphylaxis there is no prior history of sting-induced allergic reactions,' in contrast to fatal food-induced anaphylaxis, where victims have histories of multiple non-fatal prior reactions to hidden food allergens [12,13]. We also chose not to measure total serum IgE levels, because of the limited quantities of sera available,

Table 1. Distribution of venom-specific IgE antibody levels and tryptase levels in 68 cases of sudden unexpected death

Venom-specific IgE	Serum tryptase levels			Totals
	>10 ng/mL	5–10 ng/mL	<5 ng/mL	
>300%	3	1	7	11
200–300%	1	2	5	8
<200	5	3	41	49
Totals	9	6	53	68

Table 2. Clinical data from 27 cases in which an elevated tryptase or venom-specific IgE was measured

Age	Sex	Clinical circumstances	Tryptase	RAST	Autopsy
<i>Both tryptase and RAST elevated:</i>					
50	M	Found dead at home	246	1975	Atherosclerotic heart disease (ASHD)
54	F	Found dead at home	36	421	Phlebothrombosis
52	F	Lost control of car	33	266	Trauma
15	M	Fell off motorcycle	12	335	Trauma
34	M	Found gasping at home	5.6	234	ASHD
39	M	Collapsed at work	9.2	232	Fatty liver
50	M	Found dead at home	8.0	397	Hypertensive cardiovascular disease (HCVD); cerebral haemorrhage
<i>Elevated tryptase, normal RAST:</i>					
52	F	Found unresponsive at home	86	<200	Intracerebral haemorrhage
20	M	Found dead on street	14	<200	Exanguination
17	M	Found dead on street, hit by car	13	<200	Internal trauma
38	M	Lost control of car	13	<200	Internal trauma
42	M	Collapsed in airport lobby	15	<200	ASHD
21	M	Lost control of car	7	<200	Internal trauma
60	M	Found dead at home	7.4	<200	ASHD
21	M	Fell off motorcycle	5.4	<200	Internal trauma

and because of the low sensitivity and specificity of total IgE levels for diagnosis of allergic diseases [14]. Our major thrust in this study was to determine the frequency with which serum tryptase levels are increased in patients brought to the medical examiner after sudden death.

Results

Serum tryptase levels ranged from <1 to 246 ng/mL and were elevated (>5 ng/mL) in 15 of the 68 samples studied. Venom-specific IgE antibodies ranged from <200% to 3020% of the negative control and were elevated (>200% negative control) in 19 of the 68 samples studied. The distribution of tryptase values and venom-specific IgE antibody values is shown in Table 1. Using chi-square analysis, there was no statistically significant correlation between the tryptase levels and venom specific IgE antibody levels.

The clinical data from the 27 cases which an elevated tryptase or venom-specific IgE antibody was measured are shown in Table 2. The ages of these patients ranged from 15 to 60. Causes of death, as assigned by the Coronor's office, included several types of trauma in nine cases, hypertensive or atherosclerotic heart disease in four cases, haemorrhage in three cases, and epimyocarditis in one case. There were no differences in the causes of death by Coronor's diagnosis, between the cases with normal tryptase and those with elevated tryptase levels. Furthermore, the clinical circumstances

of the patients who were found to have elevated tryptase levels with or without elevated venom-specific IgE antibodies did not differ from each other; i.e. there were no clinical clues that could have been used to predict the finding of elevated levels of either tryptase or venom-specific IgE.

In 1982, the Cuyahoga County Coronor's office performed 643 autopsies in cases of death judged to be from natural causes. Of these, 57% were due to diseases of the circulatory system; none were judged to be from allergic causes, and there was no apparent seasonal fluctuation in the assigned causes.

Discussion

Anaphylactic events are rapidly progressive, are often unpredictable in occurrence, duration, and outcome, and can be fatal. While drugs, foods, and insect venoms are well recognized causes of anaphylaxis [1,2], some cases are idiopathic in origin [3]. Anaphylaxis may account for several hundred deaths per year in the United States, but specific death rates from the individual causes of anaphylaxis are estimates at best. Although risk for anaphylaxis is associated with the presence of antigen-specific IgE or with a previous immediate type hypersensitivity reaction, the occurrence of anaphylaxis cannot be predicted with certainty.

Estimates of the prevalence of insect sting allergy range from 0.4% in the general population [15] to

1.8% of all urban dwellers, to 2.9% of urban dwellers who recalled an insect sting episode [16]. Golden *et al.* [17] have reported a 33% cumulative prevalence rate of systemic reactions to hymenoptera sting. Penicillin-induced anaphylaxis has been estimated to occur in 10–15 cases per 100 000 from administrations [18–20]. There are no reliable data regarding the prevalence of anaphylaxis due to other drugs, to foods, or to other provoking factors [1,2].

Furthermore, there are at best only estimates of death rates due to anaphylaxis. There are 100–500 fatal cases of penicillin-induced anaphylaxis annually in the United States [21]. There may be 25 to 50 deaths annually in the United States due to insect sting anaphylaxis [22]. While deaths from food-induced anaphylaxis have recently been reported [12,13], there are no reliable data concerning the annual number of deaths due to food anaphylaxis [2,13].

The investigation of deaths possibly due to anaphylaxis could be facilitated by measurement of serum tryptase levels. Yunginger *et al.* [8] have reported that elevated tryptase levels in post-mortem sera reflect post-mortem mast cell activation. If used in conjunction with *in vitro* assays for allergen-specific IgE antibodies to provide evidence for pre-mortem sensitization, the aetiology, the provoking factor, and an accurate diagnosis of the cause of death might be derived. Previously, Yunginger *et al.* have provided such evidence, by finding allergen-specific IgE, exposure to the allergen, and tryptase level elevation in sera obtained within 24 h after death from 17 to 19 victims of witnessed anaphylaxis [8]. Thus, allergen-specific IgE and serum tryptase provide useful information for considering anaphylaxis as a cause of death. With these data, we re-examined sera remaining from our previous study on the prevalence of anti-venom IgE antibodies in post-mortem sera from sudden death victims.

While we do not wish to overinterpret the data, our results suggest that sudden unexpected death in adults may be caused by anaphylaxis to insect venom or other unrecognized factors more frequently than has heretofore been recognized. At a minimum, we have shown that mast cell tryptase can be detected in post-mortem sera that have been stored at -20°C for over 10 years. Evidence of substantial mast cell activation (tryptase $\geq 10\text{ ng/mL}$) was present in nine of 68 (13%) cases of sudden unexpected death despite the sera having been collected in less than ideal fashion. Although we found no overall statistically significant correlation between venom-specific IgE antibody levels in the cases studied, there was one case in which both IgE antibody and tryptase were markedly elevated. Moreover, in three additional cases, both the IgE antibody and tryptase

were moderately elevated, suggesting the possibility of insect sting-induced anaphylaxis in a small subgroup of these decedents. We did not have sufficient remaining serum to look for IgE antibodies against other potential allergens.

Inspection of the causes of death in this series, as determined by the Coroner's office, fits a pattern one might predict, with causes assigned to heart disease, trauma, liver disease and haemorrhage. We suggest that the autopsy findings, while significant anatomic facts, do not necessarily explain the immediate pre-mortem events that led to collapse, or loss of control of a car, or other such events. These can plausibly be the effects of a major allergic reaction. More detailed prospective studies involving more cases may help clarify these issues.

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