

ANATOMICAL PATHOLOGY

Anaphylactic deaths in Auckland, New Zealand: a review of coronial autopsies from 1985 to 2005

IRENE LOW AND SIMON STABLES

Department of Forensic Pathology, Auckland Hospital, New Zealand

Summary

Aims: To determine the frequency of anaphylactic deaths amongst coronial autopsy cases performed in the greater Auckland region from 1985 to 2005, and review the circumstances of death and autopsy findings.

Methods: A computerised search for anaphylactic deaths was performed using the Forensic Pathology Department database at Auckland City Hospital. Postmortem reports and police reports were reviewed to determine the circumstances of death. Details recorded included basic demographic data, medical history, agent responsible for the allergic reaction, and pathologic findings at autopsy.

Results: A total of 18 cases of anaphylactic deaths were identified for the study period, including nine males and nine females, age range 33–76 years, mean 51.9 years. There were 10 reactions to drugs or contrast media (4 anaesthetic agents, 3 antibiotic, 2 IV contrast media, 1 streptokinase), four to bee/wasp venom, two to seafood, and two undetermined. Death occurred within 1 hour of onset of anaphylaxis in 12 cases. Findings at autopsy included non-specific pulmonary oedema and congestion ($n=13$), laryngeal oedema ($n=5$), cerebral hypoxia ($n=4$) and cutaneous oedema ($n=1$). Serum tryptase levels were measured in 15 cases, and were significantly elevated ($>20\mu\text{g/L}$) in eight cases.

Conclusion: Anaphylactic reaction is an uncommon cause of sudden death. In many cases, no specific macroscopic or microscopic findings were detected at autopsy. In the presence of a typical clinical history, postmortem measurement of serum tryptase levels can be a useful diagnostic aid.

Key words: Allergy, anaphylaxis, fatalities, forensic pathology.

Received 29 December 2005, revised 26 February, accepted 3 March 2006

INTRODUCTION

Acute anaphylaxis is an uncommon but well-recognised cause of sudden death. The mechanism of death is usually attributed to either profound hypotensive shock resulting from peripheral vasodilatation, or asphyxia secondary to upper airway oedema and/or bronchospasm. The ante-mortem clinical manifestations are varied, and usually include combinations of symptoms such as generalised flushing, urticaria, angio-oedema, vomiting and diarrhoea, coughing, shortness of breath and loss of consciousness. In severe reactions, cardio-respiratory arrest can occur within minutes of symptom onset.

Postmortem diagnosis of fatal anaphylaxis is frequently hampered by the relative lack of specific pathological findings in these deaths. In some cases, laryngeal oedema, petechial haemorrhages and hyper-inflated lungs have been reported, along with non-specific visceral congestion and pulmonary oedema.¹ In many cases, no specific pathological findings are identified at autopsy. Postmortem measurements of serum tryptase levels have been proposed as a useful marker for anaphylactic deaths, although studies have shown that mild elevation in serum tryptase levels can also be seen in some non-anaphylactic deaths.²

In this study, we investigate the frequency of anaphylactic deaths amongst coronial autopsy cases performed in the greater Auckland region from 1985 to 2005. The autopsy findings reported in 18 cases of fatal anaphylaxis are described in detail.

MATERIALS AND METHODS

The Auckland Forensic Pathology Department provides coronial autopsy services to the greater Auckland region. The area covered by the service extends from Mangawhai in the North, to Huntly in the South, and includes the Hauraki Gulf islands. Details of all autopsies performed in the department since 2001 are recorded in a computerised database. The entries in this database are coded, which enabled searches for cases where anaphylaxis and anaphylactic reactions were recorded as causes of death. Five such cases were identified from 2001 to 2005. Prior to 2001, searches were performed looking for text strings that suggested anaphylaxis might have contributed to the cause of death. Thirteen cases were identified between 1985 and 2001.

For the purposes of this study, cases of anaphylactic deaths were defined as those fulfilling all of the following criteria: (1) death following documented anaphylactic reaction to a known allergenic agent, and/or findings from ancillary tests compatible with an anaphylactic reaction having occurred (particularly serum tryptase and immunoglobulin E [IgE] measurements); (2) mechanism of death compatible with that known to be associated with anaphylaxis; (3) no other cause of death apparent following a thorough autopsy examination. Cases that did not fulfil these criteria were excluded from the study.

For each case identified, the police reports and autopsy reports were reviewed to determine the circumstances preceding death. Data recorded for each case included basic demographics, medical history, presumed allergen (where identified), pathological findings at autopsy, and results of postmortem tryptase measurements.

Population data were derived from the New Zealand Census. For the purposes of this study, the population measured at the 1996 census (1 068 645) was used as the basis for calculating the incidence, as this represents the population size around the mid-point of the 20-year period covered by this study.³

RESULTS

There were 18 cases of fatal anaphylaxis identified from the Auckland Forensic Pathology Department database from 1985 to 2005. In this period, a total of 31 242 autopsies were performed. Therefore, the proportion of cases represented by anaphylactic deaths is 0.058%. The total population for the Auckland region as determined by the 1996 New Zealand Census was 1 068 645, thus the crude incidence of anaphylactic deaths is calculated at 0.08 per 100 000 population per year.

Of the 18 cases identified, 10 (56%) were reactions to drugs or intravenous contrast, four (22%) to bee stings, two (11%) to seafood, and two (11%) undetermined. In all cases where the source of allergy was identified, there was a history of collapse shortly after contact with the suspected allergen. Death occurred within 1 hour of onset of anaphylaxis in 12 cases. The mechanisms of death were attributable to sudden circulatory collapse in 10 cases in which profound hypotension was clearly documented at the time of death. In three cases, the victims survived the initial insult, but died subsequently of hypoxic brain injury. The mechanisms of death were difficult to ascertain in the remaining five cases, as these presented either with 'sudden collapse' and died before medical assessment was performed, or the deaths were unwitnessed. In 11 cases, death occurred within the hospital setting, which included five intra-operative deaths, four deaths on the intensive care wards, and two in the emergency department. In another six cases, death occurred in the community, including five at home and one in the cab of a stationary truck. Information was not available in one case.

In three of four cases of bee/wasp venom reaction, and two of two cases of seafood reaction, there were well-documented histories of previous reactions to the same allergen. None of the cases in the iatrogenic group were known to have previous allergic reactions to the agent responsible for the fatal event. Within this group, there were four reactions to anaesthetic agents, three reactions to antibiotics, two reactions to intravenous contrast, and one reaction to streptokinase. The clinical findings, separated

into four groups according to the presumed allergen, are summarised in Table 1.

The most common autopsy findings were non-specific pulmonary congestion and oedema, which were reported in 13 cases (72%). Laryngeal oedema was present in five cases (28%), while cutaneous oedema was seen in only one case (5.5%). Skin rash or petechial haemorrhages were not mentioned in any of the autopsy reports. Three of the 18 cases (17%) showed changes of global cerebral ischaemia at autopsy. In each of these three cases, there was a delay of between several hours to 3 days from onset of anaphylaxis to death. Atherosclerotic coronary vascular disease was reported in 10 cases (72%), including six cases with severe disease, two with moderate involvement, and two with mild involvement. In two cases, no positive findings relevant to the cause of death were identified at autopsy, and the diagnosis of fatal anaphylaxis was made on the basis of clinical history alone. The principal autopsy findings are summarised in Table 2.

Postmortem serum tryptase levels were measured in 15 cases, in which eight cases showed marked elevation ($>20 \mu\text{g/L}$). In another five cases, the levels were between 8.0 and $12.8 \mu\text{g/L}$. In the remaining two cases, the serum tryptase levels were reported as 'moderately elevated' in one case, and 'consistent with anaphylaxis' in another. Unfortunately, the exact levels measured in these cases were not available on review. Of the 12 cases where death occurred within 1 hour of onset of anaphylaxis, six had serum tryptase levels greater than $10 \mu\text{g/L}$, while three had levels between 8 and $9 \mu\text{g/L}$. In two cases the levels were not available, and in one case serum tryptase was not measured. Serum tryptase levels for 13 of the cases where they were available are summarised in Table 3.

DISCUSSION

Anaphylaxis is an acute, systemic type 1 hypersensitivity reaction that occurs after re-exposure to an antigen. The term 'anaphylaxis' was first defined by Charles Richet,⁴ who described the phenomenon of 'heightened sensitivity'

TABLE 1 Summary of clinical findings

	Total	Group 1: Iatrogenic	Group 2: Venom	Group 3: Seafood	Group 4: Undetermined
Total no. cases	18	10	4	2	2
Age range, years (median)	33–76 (51.9)	33–76 (53.5)	35–58 (47.7)	38–63 (50.5)	38–69 (53.5)
Male:Female	9:9	4:6	3:1	1:1	1:1
Immediate deaths (within 1 h)	12	6	4	1	1
Delayed deaths (1 h to 3 days)	6	4	0	1	1
Crude incidence (/100 000/year)	0.08	0.05	0.02	0.01	0.01

TABLE 2 Summary of autopsy findings

	Total	Group 1: Iatrogenic	Group 2: Venom	Group 3: Seafood	Group 4: Undetermined
Pulmonary congestion and oedema	13/18	5/10	4/4	2/2	2/2
Laryngeal oedema	5/18	0/10	3/4	0/2	2/2
Cutaneous oedema	1/18	0/10	0/4	0/2	1/2
Cerebral hypoxia	4/18	4/10	0/4	0/2	0/2
Atherosclerosis of coronary vessels	10/18	4/10	3/4	1/2	2/2

TABLE 3 Postmortem serum tryptase measurements in 13 cases

Tryptase levels (µg/L)	Total	Group 1: Iatrogenic	Group 2: Venom	Group 3: Seafood	Group 4: Undetermined
0–5	0/13	0/8	0/2	0/2	0/1
5–9.9	4/13	3/8	1/2	0/2	0/1
10–19.9	1/13	1/8	0/2	0/2	0/1
20–49.9	1/13	1/8	0/2	0/2	0/1
50–99.9	5/13	3/8	0/2	1/2	1/1
100–200	0/13	0/8	0/2	0/2	0/1
>200	2/13	0/8	1/2	1/2	0/1

following initial exposure to an antigen, which renders an organism more fragile and susceptible to subsequent exposures to the same antigen. It is generally regarded as a harmful reaction, which is in contrast to prophylaxis, where useful immunological protection results from prior antigen exposure.

Anaphylactic reaction is caused by cross-linkage of antigen-specific IgE molecules bound to the surfaces of tissue mast cells and peripheral blood basophils, which then undergo degranulation and release a variety of potent mediators including histamine and tryptase.⁵ Other mediators, such as certain prostaglandins and leukotrienes, are also generated via the arachidonic acid metabolism cascade. These mediators act on receptors that induce mucus production, increase vascular permeability, and stimulate smooth muscle constriction in various organs. Clinical manifestations of anaphylactic reaction can vary from organ-specific symptoms involving cutaneous, respiratory and gastrointestinal systems, such as urticaria, acute respiratory distress, abdominal pain, diarrhoea and vomiting, to laryngeal oedema and often marked facial angio-oedema. Fatal cases occur either due to severe bronchospasm with respiratory arrest, or hypotensive shock with rapid circulatory collapse, in which case death may occur prior to the onset of any other symptoms.

Epidemiological studies on life-threatening and lethal anaphylactic reactions in the United States, United Kingdom and other European countries have reported an incidence of 1–3 per 10 000 people for severe anaphylaxis, and 1–3 per million people for fatal cases.⁶ Our study, although limited in scope, demonstrated a slightly lower incidence of 0.8 per million people per year. A possible explanation for the lower incidence rate may be the fact that our study only included cases that came to coronial autopsy. Potentially, there may have been a small number of cases in which either the underlying anaphylactic nature of the illness was not recognised, and death was attributed to some other natural cause, and/or the deaths were not reported to the coroner.

The majority of cases of fatal anaphylaxis (56%) in our study were considered iatrogenic in origin. This included four cases related to anaesthesia. The exact types of anaesthetic agent responsible for the allergic reactions were not determined, although two cases were reported to have occurred during induction of anaesthesia. Of the three cases of antibiotic-induced anaphylaxis, two cases were reactions to penicillin, and one to erythromycin. None of these patients were known to have previous history of drug allergies. Bee/wasp venom allergy was the second largest group of fatal reactions in our study, with 22% of patients dying as a result of being stung. Although all four cases

were documented as bee sting reactions on the basis of clinical and eye witness history, only two cases could be confirmed, one with a raised level of specific serum IgE to honey bee, and another where the sting was retrieved from the body. Therefore, it is possible that the other two cases might have been reactions to wasp rather than bee venom.

Fatal food allergies were uncommon in our study, with only two cases identified, both of which were reactions to seafood. No cases of nut allergy were identified in our study, even though this was the most common cause of severe food allergy identified in other studies.^{5,6} Interestingly both patients in our study were known to have had previous histories of seafood allergy. In spite of this knowledge, both had knowingly consumed significant amounts of seafood shortly before their death. In one case, the patient had already presented to the emergency department on multiple previous occasions with anaphylactic reactions requiring resuscitation and administration of adrenaline.

There were proportionately many more cases with iatrogenic reactions than either food or venom reactions in our study. In comparison, a study by Pumphrey and Roberts¹ demonstrated 21 out of 56 cases were due to drug reactions, 19 cases due to bee or wasp venom reactions, and 16 cases due to food allergies, including 14 cases to nuts, one to prawns and one to nectarines. Other less common forms of allergen that have been reported to cause life-threatening anaphylaxis, such as ants, ticks, rattlesnake and hamster bites, grass pollen and hydatids⁵ were not represented in our study.

The relationship between asthma and severe anaphylactic reactions, particularly to ingested food such as nuts, cows milk and eggs, is well established. In a study by Sampson *et al.*,⁷ all 13 cases of fatal and near-fatal food anaphylaxis occurred in children and adolescents who were known asthmatics. Another study by Bock *et al.*⁸ reported 30 out of 32 cases of fatal anaphylactic reactions due to nuts. Most of the victims were adolescents or young adults, and all but one case were in asthmatics with known food allergies. The mechanisms of death were most commonly attributed to severe bronchospasm with respiratory arrest. Given the similarities in clinical presentation, it is not uncommon for anaphylactic reactions in asthmatic patients to be mistaken for severe asthma attacks.

In our study, all 18 cases were in adults, none of whom had known clinical history of asthma, and there were no cases of reactions to nuts. Microscopic changes of asthma were not identified in any of the autopsy reports. Given the fact that New Zealand's asthma prevalence is one of the highest in the developed world (30.4% of 13–14 year olds, and 25.7% of adults have symptoms⁹), it is interesting that

we did not identify any cases of anaphylactic deaths in the asthmatic population. It seems likely that some cases may have been diagnosed clinically as fatal asthma, and the underlying anaphylactic component was unrecognised at the time. Therefore, these cases most likely would not have come to coronial autopsy.

The autopsy findings of anaphylactic deaths described in this study were consistent with those reported in the literature.^{1,10} We found a significant number of cases showed only non-specific pulmonary congestion and oedema. Only five cases (28%) showed evidence of laryngeal oedema, two of which also showed increased submucosal eosinophils microscopically. The presence or absence of laryngeal oedema is largely dependent on time interval between death and subsequent autopsy. Unfortunately, information regarding the postmortem interval is not available in our study. In one case where the underlying cause of allergy was undetermined, there was marked cutaneous oedema on the face and neck. It is also interesting to note that 10 out of the 18 cases in our study showed some degree of atherosclerotic coronary vascular disease. It has been suggested that, particularly in cases of wasp or bee venom anaphylaxis, death was more likely to occur in males over the age of 50 years.¹¹ This may be related to the higher incidence of underlying cardiac and respiratory disorder in this group of patients, who would be more vulnerable to the effects of hypotension and hypoxia resulting from anaphylactic reactions. Three of the four cases of bee/wasp venom-related deaths in our study showed moderate to severe coronary atherosclerosis.

In view of the frequent absence of any specific findings at autopsies, other ancillary tests have been proposed in order to increase the diagnostic specificity of anaphylactic deaths. Of these, serum tryptase measurements have been the most widely used. As discussed earlier, the underlying mechanism of anaphylactic reaction involves degranulation of mast cells with release of histamine and tryptase. Histamine degrades too rapidly to be a useful marker of anaphylaxis. Mast cell tryptase levels on the other hand, remain relatively stable and can be detected from a few minutes up to several hours following degranulation. The peak level of serum tryptase occurs around 2 hours from onset of anaphylaxis, and then declines following first-order kinetics with a half-life of around 2 hours.¹² Therefore, blood samples should ideally be collected within hours of symptom onset. In fatal cases where there may be significant delays anticipated between time of death and autopsy, consideration should be given to collecting the sample before a formal autopsy can be conducted. In cases where death is delayed, the assay should be performed on samples taken during the acute phase of the illness. Once the sample has been collected, the tryptase levels remain relatively stable and do not appear to be significantly affected by the temperature at which samples are stored.²

Elevated levels of serum tryptase have consistently been demonstrated in postmortem samples from cases of suspected anaphylactic death.¹³ A subsequent study by Randall *et al.*,² however, demonstrated tryptase levels above the normal threshold of 1 µg/L in 31 of 49 autopsy cases in which there was no evidence to suggest anaphylactic causes for the deaths. Significantly elevated tryptase levels (>20 µg/L) were found in two cases of multiple trauma, and one case of salicylate overdose. Lesser degrees

of tryptase elevation were seen in deaths from ischaemic heart disease, aortic valve disease, pulmonary emboli, gunshot wound, and carbon monoxide poisoning. Other studies have also reported elevated tryptase levels in post-transplantation deaths, heroin deaths and some deaths attributed to SIDS. In amniotic fluid embolism, where the mechanism of death is thought to be an anaphylactoid reaction to fetal antigens, serum tryptase is often raised and can be a useful diagnostic aid.¹⁴

A study of 193 postmortem cases by Edston and van Hage-Hamsten¹⁵ looked at the optimal cut-off value for tryptase levels. They found that a level of 10 µg/L was ideal in terms of high sensitivity (86%) and specificity (88%). Therefore, serum tryptase measurements are useful in the evaluation of sudden unexplained deaths, particularly when the clinical history is suggestive of an anaphylactic reaction. A raised serum tryptase level on its own, however, is not diagnostic of fatal anaphylaxis. In our laboratory, a higher threshold is employed in order to maximise the specificity of the test. In our case, a serum tryptase level of <10 µg/L is considered negative, 10–20 µg/L is borderline and possibly suggestive of anaphylaxis, while >20 µg/L is considered a positive test and strongly suggestive of anaphylaxis.

In our study, serum tryptase levels were elevated to varying degrees in all 15 cases where they were measured. In eight of these, the levels were over 20 µg/L. Of the three cases in which serum tryptase was not measured, two were from 1985 when the test was not available. In the third case, which was from 1994, the diagnosis of anaphylaxis was made on the basis of clinical history alone.

Postmortem blood samples can also be used to measure total IgE and antigen-specific IgE by the radio-allergo-sorbent technique (RAST).¹⁶ This may be useful for assessing any underlying atopic disposition, and identify the degree to which a patient has been sensitised to a particular antigen. In living patients, a combination of skin prick tests and/or RAST are performed to identify potential allergens for which immunotherapy may be administered. This is particularly useful in patients who have had anaphylactic reactions to insect venom. In our study, only one case had RAST performed on a postmortem blood sample, which confirmed the presence of significant sensitisation to bee venom in a patient who died of suspected bee-sting anaphylaxis.

In conclusion, we have reported the first study on anaphylactic deaths based on coronial autopsies performed in Auckland, New Zealand. Our findings are largely consistent with those reported in other international studies and confirm that anaphylaxis is an uncommon cause of sudden death. Iatrogenic reactions play the major role in causing fatal anaphylaxis, with venom and food reactions being less common causes in this study. Autopsy findings are often non-specific, and serum tryptase measurements can be a useful diagnostic test when the clinical history is compatible with fatal anaphylaxis.

ACKNOWLEDGEMENT The authors thank Dr Timothy Kolemeyer (Department of Forensic Pathology, Auckland Hospital) for his advice and assistance with preparation of the manuscript.

Address for correspondence: Dr I. Low, Department of Forensic Pathology, LabPlus, Auckland City Hospital, PO Box 110031, Auckland, New Zealand. E-mail: irenel@adhb.govt.nz

References

1. Pumphrey RSH, Roberts SD. Postmortem findings after fatal anaphylactic reactions. *J Clin Pathol* 2000; 53: 273–6.
2. Randall B, Butts J, Halsey JF. Elevated postmortem tryptase in the absence of anaphylaxis. *J Forensic Sci* 1995; 40: 208–11.
3. Cook L. *New Zealand – A Regional Profile: Auckland*. Wellington: Statistics New Zealand, 1999.
4. Richet C. Nobel Lecture, December 11, 1913. *Nobel Lectures, Physiology or Medicine 1901–1921*. Amsterdam: Elsevier Publishing Company, 1967.
5. Rusznak C, Peebles RS. Anaphylaxis and anaphylactoid reactions – A guide to prevention, recognition and emergent treatment. *Postgrad Med* 2002; 111: 101–14.
6. Moneret-Vautrin DA, Morisset M, Flabbee J, et al. Epidemiology of life-threatening and lethal anaphylaxis: a review. *Allergy* 2005; 60: 443–51.
7. Sampson HA, Mendelson L, Rosen JP. Fatal and near-fatal anaphylaxis to food in children and adolescents. *N Engl J Med* 1992; 327: 380–4.
8. Bock SA, Munoz-Furlong A, Sampson HA. Fatalities due to anaphylactic reactions to food. *J Allergy Clin Immunol* 2001; 107: 191–3.
9. Wickens K, Fitzharris P, Crane J. Increasing asthma prevalence in New Zealand: understanding the causes. *The New Zealand Public Health Report* 1998; 5 (3): 17–20.
10. Riches KJ, Gillis D, James RA. An autopsy approach to bee sting-related deaths. *Pathology* 2002; 34: 257–62.
11. Harvey P, Sperber S, Kette F, et al. Bee-sting mortality in Australia. *Med J Aust* 1984; 140: 209–11.
12. Schwartz LB, Yunginger JW, Miller J, et al. Time course of appearance and disappearance of human mast cell tryptase in the circulation after anaphylaxis. *J Clin Invest* 1989; 83: 1551–5.
13. Yunginger JW, Nelson DR, Squillace DL, et al. Laboratory investigations of deaths due to anaphylaxis. *J Forensic Sci* 1991; 36: 857–65.
14. Marcus BJ, Collins KA, Harley RA. Ancillary studies in amniotic fluid embolism – a case report and review of the literature. *Am J Forensic Med Pathol* 2005; 26: 92–5.
15. Edston E, van Hage-Hamsten M. β -Tryptase measurements post-mortem in anaphylactic deaths and in controls. *Forensic Sci Int* 1998; 93: 135–42.
16. Schwartz HJ, Squillace DL, Sher TH, et al. Studies in stinging insect hypersensitivity: Postmortem demonstration of antivenom IgE in possible sting-related sudden death. *Am J Clin Pathol* 1986; 85: 607–10.