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Angioedema deaths in the United States, 1979–2010

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ABSTRACT

Background: Hospital admission data indicate that the angioedema incidence has increased during the past several decades. Little is known about mortality trends.

Objectives: To count the number of deaths associated with angioedema in the United States, investigate correlations with age, sex, race, and other contributory causes, and analyze trends from 1979 to 2010.

Methods: All US death certificates in which angioedema was listed as an underlying or contributing cause of death during 1979 to 2010 were analyzed. Age-adjusted mortality rates were analyzed by age, sex, and race. Other conditions designated as the underlying cause of death were investigated.

Results: From 1979 to 2010, there were 5,758 deaths in which angioedema was listed as a contributing cause. The age-adjusted death rate for hereditary angioedema decreased from 0.28 (95% confidence interval [CI] 0.25–0.32) to 0.06 (95% CI 0.05–0.08) per million persons per year. Conversely, mortality for angioedema increased from 0.24 (95% CI 0.21–0.27) to 0.34 (95% CI 0.31–0.37) per million. Blacks constituted 55% of angioedema deaths that were associated with use of angiotensin-converting enzyme inhibitors. On death certificates that listed hereditary angioedema as the underlying cause of death, cancer (frequently lymphoma or leukemia) was the second most commonly listed cause.

Conclusion: Angioedema-associated deaths were very rare from 1979 to 2010. Hereditary angioedema deaths became even more so, whereas nonhereditary angioedema deaths increased. Risks associated with angiotensin-converting enzyme inhibitors were higher in blacks. Lack of specific coding for acquired angioedema most likely explains the observed association between cancer and hereditary angioedema. In the future, more granular coding systems may help distinguish hereditary from acquired angioedema.

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Introduction

Angioedema is a rapid-onset, transient, asymmetric, localized subcutaneous, and mucosal swelling that can affect the face, mouth, tongue, throat, extremities, bowel, and genitalia. Episodes can be triggered by medications, foods, or even sun exposure, although most cases remain idiopathic.

Hereditary angioedema (HAE) is an inherited deficiency of C1 inhibitor and is clinically similar to acquired angioedema (AAE). Thus, a significant challenge in diagnosis arises because the appearance of the angioedema itself cannot point toward a specific etiology.¹

Hereditary angioedema has been estimated to affect 1 in every 50,000 persons,^{2–4} and AAE has been reported to affect 200 individuals worldwide.⁵ Hospital admission data have indicated that all-cause angioedema incidence has increased during the past

several decades, and US estimates of annual emergency department visits for angioedema of all types have reached more than 108,000.⁶

However, there is little evidence on mortality trends of angioedema. Thus, the objectives of this study were to count the number of angioedema-associated deaths in the US general population, investigate associations with age, sex, race, and other contributory causes, and analyze trends from 1979 to 2010. The Centers for Disease Control and Prevention (CDC) consider HAE a valid underlying cause of death on US death certificates; however, nonhereditary angioedema is not; therefore, the authors sought to determine which underlying causes were most often recorded for these individuals.

Methods

This study was exempt from institutional review board approval. Information was extracted from US death certificates from 1979 to 2010 using the CDC's Multiple Cause of Death compressed mortality files. Death certificates contain information on age, sex, race, and other demographic data and information on

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place and causes of death. The medical certification of cause of death can be made only by a qualified person, such as a physician, a medical examiner, or a coroner. Causes of death were coded according to the *International Classification of Diseases, Ninth Revision* (ICD-9) and the *International Classification of Diseases, Tenth Revision* (ICD-10) from 1979 to 1998 and from 1999 to 2010, respectively. For all years from 1979 to 2010, the death certificate can list up to 20 causes that contributed to death. The disease that initiated the events resulting in death is denoted as the underlying cause.

The present study sample was comprised of all death certificates from 1979 to 2010 with codes corresponding to angioedema (ICD-9 995.1, ICD-10 T78.3) and those from 1999 to 2010 with codes corresponding to HAE (ICD-10 D84.1). Because angioedema can be misdiagnosed, codes for urticaria (ICD-9 708, ICD-10 L50) were included.

The relative proportions of deaths by race and place of death were computed, and the most commonly observed medical conditions and external causes noted as the underlying causes of death were summarized. Cause-specific mortality rates were calculated by dividing the total number of deaths by the midyear population totals for the US general population. Age-adjusted death rates were calculated using the 2000 US standard population. To investigate trends over time, age-adjusted death rates were compared over the course of the study period.

In the estimation trends, it is important to consider possible changes to case definition criteria. In this regard, the coding schemes for angioedema and urticaria were specific and remained unchanged from ICD-9 to ICD-10. In contrast, the specificity of the coding of HAE changed considerably from ICD-9 to ICD-10. That is, ICD-9 code 277.6 corresponds to HAE or any of several other deficiencies in circulating enzymes (including β -ketothiolase, biotinidase, holocarboxylase synthetase, and myoadenylate deaminase, in addition to acquired C1 inhibitor deficiency or AAE), whereas the ICD-10 code D84.1 is specific to HAE or defects in the complement system (and does not include the aforementioned circulating enzymes but may still include an acquired deficiency of

C1 inhibitor). Therefore, HAE deaths only from 1999 to 2010 were analyzed when the more specific ICD-10 code was used.

Statistical 95% confidence intervals (CIs) for the estimated rates were computed under the assumption that death counts followed a Poisson distribution.

Results

The authors identified 600 deaths associated with HAE (or defects of the complement system) from 1999 to 2010. There were 1,042 angioedema or urticaria deaths during the same period, and an additional 675 angioedema or urticaria deaths during the earlier period from 1979 to 1998. There were 7 cases in which HAE and angioedema or urticaria were listed on the death certificate from 1979 to 2010. There were 100 deaths in which angioedema and asphyxiation were reported from 1979 to 2010; 53 of these deaths occurred in an inpatient medical facility, 15 at an outpatient medical facility or emergency department, and 5 were dead on arrival.

Hereditary Angioedema

From 1999 to 2010, there were 600 death certificates that listed ICD-10 code D84.1 for HAE or defects of the complement system as a contributing or underlying cause of death (Table 1). (For completeness, the authors note that from 1979 to 1998 there were 3,448 death certificates that listed ICD-9 code 277.6 for HAE, defects of the complement system, or deficiencies of other circulating enzymes.) The age-adjusted HAE death rate was very low at only 0.17 (95% CI 0.15–0.18) per million persons per year. Furthermore, there was a clinically notable and statistically significant decrease in the death rate from 0.28 (95% CI 0.25–0.32) in 1999 to 2002 to 0.06 (95% CI 0.05–0.08) per million persons per year in 2007 to 2010. The most commonly listed underlying cause of death was HAE (45%). The next most frequent underlying cause of death was cancer (27%), the most common of which was leukemia or lymphoma. Most HAE deaths (83%) occurred in inpatient hospital settings. Mortality rates increased with advancing age, and there was no

Table 1
Hereditary angioedema (and complement system deficiency) deaths in the United States, 1999 to 2010

Year	ICD-10 ^a			
	1999–2002	2003–2006	2007–2010	1999–2010
Deaths, n	319	202	79	600
Mortality rate (per million)	0.28	0.17	0.06	0.17
95% Poisson confidence interval	0.25–0.31	0.15–0.20	0.05–0.08	0.16–0.18
Age-adjusted rate (per million)	0.28	0.17	0.06	0.17
95% Poisson confidence interval	0.25–0.32	0.15–0.19	0.05–0.08	0.15–0.18
Underlying cause of death, %				
Hereditary angioedema or other deficiency of circulating enzymes	43	47	49	45
Circulatory disease	4	4	6	4
Respiratory disease	3	1	3	3
Cancer	27	27	20	26
Place of death, %				
Hospital, clinic, or medical center	82	86	77	83
Inpatient	77	80	63	76
Outpatient or emergency department	4	5	13	6
Hospital, dead on arrival	0	0	1	0
Other care facility	10	5	4	8
Age (y) (crude rates)				
0–14	0.05	0.03	0.01	0.03
15–34	0.06	0.04	0.03	0.04
35–64	0.28	0.21	0.08	0.19
65–84	1.07	0.49	0.18	0.57
≥85	2.05	1.02	0.24	1.04
Female patients (age-adjusted rates)	0.23	0.13	0.05	0.13
Male patients (age-adjusted rates)	0.35	0.21	0.08	0.21
Black patients (age-adjusted rates)	0.33	0.20	0.13	0.21
White patients (age-adjusted rates)	0.28	0.17	0.06	0.16

Abbreviation: ICD-10, *International Classification of Diseases, Tenth Revision*.

^aICD-10 codes: hereditary angioedema or other deficiencies of the complement system, D84.1; unspecified accident or exposure, X58 and X59; adverse effect of therapeutic drugs, Y40 to Y59; circulatory disease, I00 to I99; respiratory disease, J00 to J99; neoplasms, C01 to D49.

significant racial difference in age-adjusted rates (0.16 [95% CI 0.15–0.18] and 0.21 [95% CI 0.17–0.27] per million persons per year for whites and blacks, respectively).

Angioedema and Urticaria

From 1979 to 2010, there were 1,717 death certificates that listed angioedema (1,436) or urticaria (293) as a contributory cause; 12 of these noted angioedema and urticaria. From 1979 to 1998, there were 675 deaths, for an age-adjusted rate of 0.15 (95% CI 0.14–0.16) per million persons per year (Table 2). There was a modest increase from 0.13 (95% CI 0.10–0.16) per million in 1979 to 1982 to 0.17 (95% CI 0.15–0.20) per million persons per year in 1995 to 1998. Mortality rates increased with age and were marginally higher for men than for women. These findings could reflect differences in prevalence or mortality. Sex differences in mortality for persons with angioedema cannot be inferred directly. There was a significant difference in age-adjusted mortality rates by race, with 0.13 (95% CI 0.11–0.14) per million for whites and 0.39 (95% CI 0.33–0.46) for blacks. The most common setting was the inpatient hospital locale (41%), although it is notable that 21% of deaths were recorded in the outpatient setting, emergency department, or were dead on arrival to the hospital. The most common reported underlying cause of death was an unspecified exposure in 20% and adverse effects of therapeutic drugs in the other 10%. Circulatory disease was the next most frequent underlying cause (28%).

In the later period, from 1999 to 2010, there were 1,042 deaths, for an age-adjusted rate that was nearly twice that of the early period at 0.29 (95% CI 0.27–0.31) million persons per year. There was a significant increase from 0.24 (95% CI 0.21–0.27) per million persons per year in 1999 to 2002 to 0.34 (95% CI 0.31–0.37) per

million persons per year in 2007 to 2010. The mortality rates increased with age and were significantly higher for blacks at 1.00 (95% CI 0.89–1.11) per million than for whites at 0.21 (95% CI 0.20–0.23). There was no sex difference in age-adjusted rates. The inpatient hospital location was the most common setting for death (61%), and 16% were noted to occur in the outpatient or emergency department setting or were dead on arrival. Like the earlier period, external injury or poisoning was listed as the underlying cause in most cases (53%). In particular, 46% were attributed to unspecified accidents or exposures, and 7% were attributed to adverse effects of therapeutic drugs. Circulatory disease was the next most frequent underlying cause of death (19%).

Over the course of the entire study period, from 1979 to 2010, there were 136 death certificates (8%) noting angioedema or urticaria in which the underlying cause of death implicated was a therapeutic drug. Forty-five percent of these drug-associated deaths occurred in blacks. Of the 18 cases in which angiotensin-converting enzyme (ACE) inhibitors were implicated specifically, 55% were in black patients. In contrast, blacks constituted only 39% of total angioedema or urticaria deaths. There were 364 deaths (21%) in which hypertensive diseases (ICD-9 codes 401–405, ICD-10 codes I10–I15) played contributing roles. The age-adjusted mortality rate was significantly higher in blacks at 0.19 (95% CI 0.16–0.23) per million than that for whites at 0.03 (95% CI 0.03–0.03) per million.

Discussion

This is the first US population-based study of angioedema-related mortality. The authors found that the number of

Table 2
Angioedema- or urticaria-related deaths in the United States, 1979 to 2010

Year	ICD-9 ^a					ICD-10 ^b				
	1979–1982	1983–1986	1987–1990	1991–1994	1995–1998	1979–1998	1999–2002	2003–2006	2007–2010	1999–2010
Deaths, n ^c	104	107	141	143	180	675	268	336	438	1042
Angioedema	75	79	111	118	142	525	227	303	381	911
Urticaria	32	28	30	26	38	154	42	37	60	139
Mortality rate (per million)	0.11	0.11	0.14	0.14	0.17	0.14	0.24	0.29	0.36	0.30
95% Poisson confidence interval	0.09–0.14	0.09–0.14	0.12–0.17	0.12–0.16	0.14–0.19	0.13–0.15	0.21–0.27	0.26–0.32	0.33–0.39	0.28–0.31
Age-adjusted rate (per million)	0.13	0.13	0.15	0.15	0.17	0.15	0.24	0.28	0.34	0.29
95% Poisson confidence interval	0.10–0.16	0.10–0.15	0.13–0.18	0.12–0.17	0.15–0.20	0.14–0.16	0.21–0.27	0.25–0.31	0.31–0.37	0.27–0.31
Underlying cause of death, %										
Unspecified accident or exposure	9	17	17	30	24	20	45	45	48	46
Adverse effects of therapeutic drugs	14	8	12	12	6	10	5	8	6	7
Circulatory disease	28	33	30	21	29	28	22	21	16	19
Respiratory disease	7	7	5	2	9	6	6	5	4	5
Cancer	3	3	5	5	7	5	7	5	3	5
Place of death, %										
Hospital, clinic, or medical center	68	68	82	72	68	72	78	80	76	78
Inpatient	31	36	44	45	46	41	59	63	62	61
Outpatient or emergency department	6	13	21	20	17	16	16	17	14	15
Hospital, DOA	8	5	5	6	4	5	1	1	1	1
Other care facility	6	10	2	10	13	9	12	9	12	11
Age (y) (crude rates)										
0–14	0.00	0.00	0.02	0.04	0.02	0.01	0.00	0.00	0.04	0.01
15–34	0.07	0.03	0.05	0.03	0.02	0.04	0.03	0.04	0.05	0.04
35–64	0.12	0.10	0.12	0.13	0.11	0.12	0.19	0.27	0.30	0.25
65–84	0.37	0.51	0.53	0.52	0.67	0.53	0.95	1.08	1.42	1.16
≥85	1.19	1.33	1.79	1.85	2.92	1.92	3.57	3.28	3.97	3.63
Female patients (age-adjusted rates)	0.09	0.10	0.14	0.12	0.16	0.13	0.25	0.26	0.34	0.28
Male patients (age-adjusted rates)	0.17	0.16	0.17	0.17	0.19	0.17	0.22	0.32	0.32	0.29
Black patients (age-adjusted rates)	0.27	0.18	0.42	0.43	0.58	0.39	0.69	1.02	1.24	1.00
White patients (age-adjusted rates)	0.11	0.12	0.13	0.12	0.14	0.13	0.19	0.21	0.24	0.21

Abbreviations: DOA, dead on arrival; ICD-9, *International Classification of Diseases, Ninth Revision*; ICD-10, *International Classification of Diseases, Tenth Revision*.

^aICD-9 codes: angioneurotic edema, 995.1; urticaria, 708; unspecified accident or exposure, 928.8 and 928.9; adverse effect of therapeutic drugs, 930 to 949; circulatory disease, 390 to 459; respiratory disease, 460 to 519; neoplasms, 140 to 239.

^bICD-10 codes: angioneurotic edema, T78.3; urticaria, L50; unspecified accident or exposure, X58 and X59; adverse effect of therapeutic drugs, Y40 to Y59; circulatory disease, I00 to I99; respiratory disease, J00 to J99; neoplasms, C01 to D49.

^cThere were 12 cases in which urticaria and angioneurotic edema were listed on death certificates.

angioedema-associated deaths was very small, with fewer than 2,000 from 1999 to 2010.

For HAE (or other defects of the complement system), 600 deaths were identified over the 12-year period from 1999 to 2010. This corresponds to approximately 50 HAE deaths in the whole of the United States each year. Various sources have suggested the HAE prevalence to be 1 per 50,000 population.^{2–4} Recent US population estimates have suggested a total population of 300 million with an age-adjusted death rate of 850 per 100,000. Under somewhat broad assumptions, in a given year one might expect to see 6,000 HAE cases, of whom roughly 50 would be expected to die. The authors found 50 deaths per year, which provides some independent confirmation of the HAE prevalence estimates reported in the literature.

The already very low age-adjusted HAE mortality rate decreased nearly 4-fold from the early to late 2000s. The reasons for this are not entirely clear but may be related to improved awareness, diagnosis, and management. Before the introduction of effective therapies for HAE, one third of patients died of asphyxiation.⁷ Mortality has been reported to occur in 214 of 728 patients diagnosed with HAE owing to C1 inhibitor deficiency in Germany; 70 of these deaths were from asphyxiation during a laryngeal attack.⁸ C1 inhibitor replacement was shown to be efficacious in the treatment and prophylaxis of HAE attacks in 1996,⁹ and by 2009 several safe and effective drugs, such as human nanofiltered plasma-derived C1 inhibitor (Cinryze; AbbVie, North Chicago, Illinois), pasteurized plasma-derived C1 inhibitor (Berinert; CSL Behring, King of Prussia, Pennsylvania), and ecallantide (Kalbitor; Dyax Corporation, Cambridge, Massachusetts), to treat and prevent HAE became readily available.¹⁰ In addition, icatibant, a bradykinin B₂ receptor antagonist (Firazyr; AbbVie), has been shown to be effective.¹¹ Increased use of these newer therapies also might explain the decrease in the HAE mortality rate, because a survey of physicians taking care of approximately 900 patients with HAE in 2009 and 2010 showed that approximately 50% of physicians were familiar with and likely to use new HAE therapies.¹²

Acquired C1 inhibitor deficiency can pose a significant challenge in diagnosis because it encompasses an array of clinical scenarios, and the appearance of the angioedema cannot point toward a specific etiology.¹ Furthermore, it is difficult to distinguish from HAE without details of the age of onset, family history, serologic evidence of defects in the complement system (including C1q) and autoantibodies, and confirmation with genetic testing of SERPING1.¹ The total reported cases of AAE worldwide number fewer than 200.⁵ One report estimated that for every 12 patients diagnosed with HAE, there is 1 patient diagnosed with AAE.¹³ The authors found that 26% of death certificates that noted ICD-10 code D84.1 also had cancer listed as the underlying cause. Closer inspection disclosed that most of these deaths were caused by leukemia or lymphoma. Associations between chronic lymphocytic leukemia and lymphomas and AAE have been reported in the literature,^{14,15} although no such associations have been reported for HAE. There is low likelihood that cancer is associated with HAE. Lack of coding specificity for AAE most likely explains the apparent association between malignancy and HAE, because ICD-10 code D84.1 includes HAE and an acquired deficiency of C1 inhibitor (AAE).

Unlike in HAE, the death rates associated with angioedema or urticaria increased significantly during the study period. It is noteworthy that, according to CDC coding rules, angioedema is not considered a valid underlying cause of death. External causes, namely unspecified exposures or adverse effects of therapeutic drugs, were the most common reported underlying causes actually listed on death certificates. Diseases of the circulatory system were the second most common. In this study, there were only 12 deaths (of 1,717) in which urticaria and angioedema were listed. Therefore,

angioedema mortality was infrequently associated with the additional diagnosis of urticaria, which suggests that the fatal cases of angioedema were not chronic cases of urticaria. This is consistent with other research that has found that angioedema associated with ACE inhibitors rarely presents with urticaria.¹⁶

The increase in angioedema-associated deaths mirrors trends toward increased hospitalizations for angioedema in the United States.¹⁷ Studies abroad also have shown an increase in angioedema hospitalizations,¹⁸ and these might be attributed to the increased use of ACE inhibitors.¹⁹ Yearly angioedema hospitalizations have been shown to be consistently higher for black patients than for others.²⁰

Some researchers have hypothesized that the increased incidence of angioedema is influenced at least in part by increased usage of ACE inhibitors, first introduced in 1981 for the control of hypertension.²¹ Angioedema has been reported in approximately 0.1% to 2.2% of patients treated with ACE inhibitors,^{22,23} with a higher incidence occurring in women and blacks.^{24,25} From 2001 to 2009, there were 979,342 emergency department visits for angioedema, and having hypertension or black race was associated with admission.⁶ In the present study, most angioedema-associated deaths had reported unspecified accidents or exposures as the underlying causes of death, but 7% to 10% were specifically associated with the use of therapeutic drugs. Before the approval of C1 inhibitor therapy for use by the Food and Drug Administration, androgenic hormone derivatives such as danazol were used. Adverse effects included hyperlipidemia and transaminase elevation, which might explain a decrease in angioedema-associated mortality with the introduction of C1 inhibitor as the mainstay of therapy. Furthermore, these data were not sufficient to confirm whether there has been a trend in angioedema associated with ACE inhibitors in particular. However, the listing of hypertension as a contributing cause on 21% of the angioedema death certificates suggests a possible role for the use of ACE inhibitors.

Although most angioedema-related deaths (61%) were observed in whites, most deaths (55%) in which ACE inhibitor exposure was noted as the underlying cause were observed in blacks. A possible explanation for this is an increased sensitivity to bradykinin in black patients taking ACE inhibitors.²⁶

Limitations

The present findings must be interpreted in light of the limitations associated with death certificate-based research. Most notable is the relative lack of specificity in ICD coding for HAE, AAE, other defects of the complement system, or deficiencies in circulating enzymes. ICD-10 D84.1 codes for HAE and defects of the complement system but is still inclusive of an acquired deficiency of C1 inhibitor. Thus, there may have been some over-counting of HAE deaths. As noted earlier, the 26% of death certificates with cancer noted as the underlying cause actually might have been associated with AAE. Conversely, the estimated incidence of approximately 50 HAE deaths per year is broadly consistent with the HAE prevalence estimates in the literature. The problem of specificity is more extreme for deaths from 1979 to 1998, when ICD-9 code 277.6, which included “other deficiencies of circulating enzymes,” was used. Because of this, the authors were unable to report on death rates and trends for HAE during this earlier period.

In addition, the authors recognize that misdiagnosis and mis-coding could have influenced the results. For example, only 100 deaths occurred in which angioedema and asphyxiation were reported. The authors believe the discrepancy between the relatively large number of angioedema deaths and the contrastingly small number of asphyxiation deaths could reflect mis-recording of the underlying cause of death as “respiratory” in nature as opposed to asphyxiation. In addition, “non-forensic” trained health care

professionals participate in the “forensic” process of completing death certificates; therefore, the direct mechanism of death is not always listed as the first diagnosis. Because the CDC recognizes HAE as a valid underlying cause of death, in these cases asphyxiation might not have been listed only as a contributing cause rather than the underlying cause of death. To be comprehensive (ie, to increase the sensitivity of angioedema case ascertainment), the diagnosis of urticaria was included in this analysis of angioedema. These cases were by far the minority and did not affect the results related to trends over time.

Moreover, although all contributing causes of death from the original certificates are listed in the CDC’s compressed mortality database, the coding process used to determine the underlying cause of death excludes angioedema and other potentially allergic etiologies such as anaphylaxis. Other reports comparing anaphylaxis-related deaths based on death certificates with hospital discharges have concluded that anaphylaxis might be underreported by the 2 sources.^{27,28} The rationale provided by the CDC is that such conditions reflect symptoms rather than an underlying disease per se. Many clinicians and their patients, especially those who have experienced angioedema, may disagree with this. Furthermore, such exclusions may explain in part why there have been no population-based studies of angioedema mortality until now.

Conclusions

Angioedema-related mortality is very rare. The present data suggest that deaths attributed to HAE are becoming even rarer, whereas deaths associated with angioedema are increasing. On the one hand, there have been improvements in awareness of angioedema and its management. On the other hand, the increasing usage of medications such as ACE inhibitors might induce angioedema attacks, especially in black patients. Lack of specific coding for AAE most likely explains the observed association between cancer and HAE, because the current diagnosis code for HAE includes AAE. In the future, more granular coding systems could help distinguish HAE cases from other cases of angioedema, including AAE.

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