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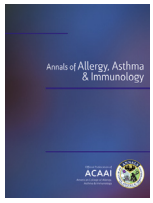

Angioedema deaths in the United States, 1979–2010

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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.

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.*

[a]ICD-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.