Clinical Communications

Life expectancy in Italian patients with hereditary angioedema due to C1-inhibitor deficiency

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for C1 inhibitor Angioedema)

Clinical Implications

- In Italian patients with hereditary angioedema, life expectancy is the same as that of the general population, and laryngeal edema is not the main cause of death.

C1-inhibitor (C1-INH) deficiency due to mutation in the *SERPING1* gene is the most common cause of hereditary angioedema (HAE).[1] C1-INH-HAE occurs worldwide; its prevalence in Italy has been calculated to be 1:64,000.[2] It is characterized by self-limiting edema of the extremities, face, genitals, and gastrointestinal and upper airway mucosae, in absence of urticaria. Attacks that involve the upper airways place patients at risk of asphyxiation.[3] The mortality related to C1-INH-HAE depends on the presence of correct diagnosis and availability of on-demand treatment. In a previous earlier retrospective observation in Italian families,[4] it has been recorded that more than 50% of subjects could have died of laryngeal edema. A survey in Germany confirms that a correct diagnosis drastically reduced the disability of laryngeal edema. Nevertheless, even in diagnosed patients, asphyxiation remained a common cause of death.[5] There are no studies assessing life expectancy and cause of death in patients with C1-INH-HAE.

An Italian database showed that male patients older than 70 years were represented in a reduced proportion compared with the general population; however, this survey did not consider the causes of death.[2] Here, we analyzed patients followed at Italian centers for C1-INH-HAE to compare their life expectancy and causes of death with those of Italian residents. We included a cohort of patients diagnosed from 1973 data collected by the ITAlian network for C1-INH-HAE in the HAE Global Registry (ClinicalTrials.gov NCT03828279). The Local Ethic Committee gave approval to the study. Diagnosis was based on personal and/or family history of angioedema and functional and/or antigenic plasma levels of C1-INH less than or equal to 50% of normal.[6] Data regarding the causes of death were extracted from medical records rather than death certificates and integrated by telephone interviews to relatives and analyzed for life expectancy. All collected data were compared with data of the Italian Institute of Statistics on Italian residents.

Descriptive statistical analysis was performed and reported as mean, median, SD, range, and distribution percentage. Mortality rate compares actual versus expected number of deaths in a population observed for a specific interval of time (observed person per year [OPY]). To assess this parameter, the study population was clustered in time intervals of 5 years. Statistical significance of differences between actual and expected deaths was calculated as standardized mortality rate (SMR) expressed as percentage and CIs.

Until March 2018, the study population consisted of 1113 patients; 90 died during the observation. Mean age at death considering the entire period of observation was 69.6 years in females and 64.3 in males; median age at diagnosis was 28.1 years (0-88), and median age at death was 73.5 years for females and 72.8 for males (Figure 1). The mean age at death, grouped by sex in the period 2011 to 2017, was 78.2 years for females versus 72.6 for males in the study population and 82.9 versus 77.4 in Italian residents.

OPY progressively grew: 39 in the period 1970 to 1975, 4519 in the period 2011 to 2015, and 20530 for the entire period. Sixty-nine percent of OPY were from 2000 onward and 72% of deaths (65 of 90) occurred in the same period. On calculating age-specific mortality of Italian residents in comparable years, we found that the expected number of deaths in the study population was 54.4 in females and 39.8 in males. Observed numbers were 43 in females (SMR = 79%) and 47 in males (SMR = 118%). Differences between expected and observed numbers did not reach statistical significance for either sex (females: CI 55% <SMR <103%; males: CI 84% <SMR <152%).

Table I reports the cause of death in 88 patients. In 2 patients the cause of death was not available.

Neoplasms, detected in 28 (17 males) subjects, were the most frequent cause of death. Liver carcinoma represented 19.2% of all malignancies, and hepatitis C virus infection was present in 3 of 5 patients who died from this neoplasia. Cerebrovascular disease (including cardiac disease) was present in 21 (12 males) subjects, representing the second most frequent cause of death. Laryngeal edema was the cause of death in 5 patients, occurring in 1983, 1985, 2001, and 2007 (for 2 patients), respectively. They were 64, 61, 34, 44, and 52 years old, respectively. Lifesaving treatment was not available for the first, third, and fourth patients (the third moved to an incoming country without medication, and the fourth was affected by a psychiatric condition and refused to have treatment at home). In the other 2 cases, the treatment was delayed for hours (1 delayed access to the emergency department, 1 unavailabile venous access because of severe obesity).

In this survey, life expectancy was not significantly different in comparison with the general population.

Leading causes of death in patients with HAE were malignancy and cardiovascular disease, whereas in the general population the cardiovascular mortality was more frequent (40%)
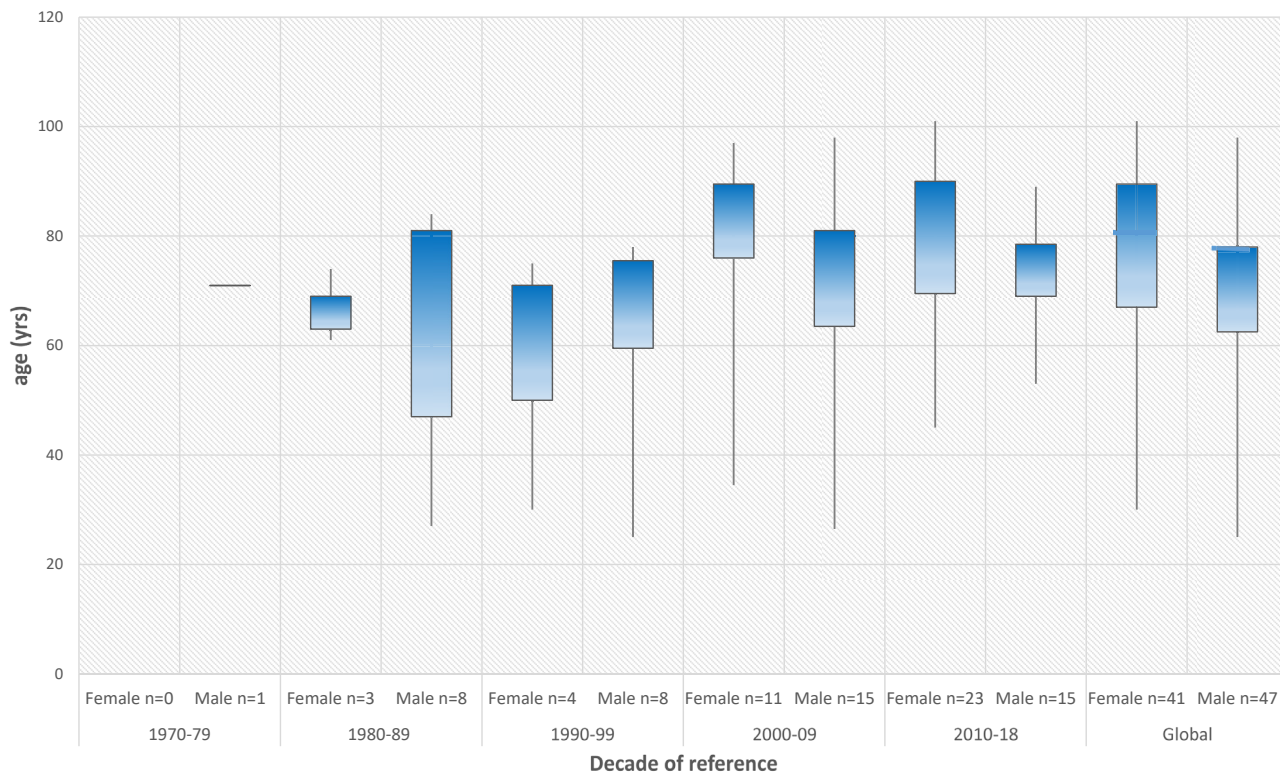
FIGURE 1. Age at death by decade by sex in patients with C1-INH-HAE. The lower and upper limits of the vertical bars express minimum and maximum age, respectively. The lower and upper limits of the boxes express the first and third quartiles of age distribution, respectively. Global median age is indicated inside the boxes.

TABLE I. Cause of death and presence of long-term prophylaxis with AA in 88 patients with C1-INH-HAE.

Cause of death	Females	Males	AA	No AA
Lung cancer	2	5	2	5
Liver cancer	1	4	0	5
Gastrointestinal cancer	1	3	2	2
Pancreas cancer	2	1	1	2
Other malignancies	3	4	1	6
Myocardial infarction	2	8	4	6
Cardiac failure	4	2	3	3
Cachexia	5	1	2	4
Cerebrovascular disease	3	2	4	1
Edema of the larynx	4	1	1	4
Pneumonia	3	1	0	4
Trauma	2	2	3	1
Dementia	3	0	2	1
Chronic bronchitis	1	2	2	1
Inhalation pneumonia	2	0	1	1
Liver cirrhosis	0	2	0	2
Renal failure	0	2	1	1
Heroin poisoning	1	1	1	1
Others diseases*	4	4	5	3
Total	43	45	35	53

*Recurring in single patients.

compared with the cancer-related mortality (29%). Asphyxiation was less common than previously reported. C1-INH-HAE is considered life-threatening in case of laryngeal attacks, and laryngeal edema was earlier reported as the first cause of death in patients with C1-INH-HAE.[6,7] Plasma-derived C1-INH has been available to the patients since 1985.[8] We conclude that

upon availability and appropriate use of on-demand treatment, asphyxiation is not the leading cause of death in patients with C1-INH-HAE.

A significant portion of our population has been exposed to long-term treatment with attenuated androgens (AA), which are supposed to increase the risk of hepatic neoplasia. The fact that none of the patients with liver cancer had been on AA suggests that such treatment may not be related to increased risk for liver malignancies. However, comparisons between patients with and without AA bear a risk of bias (eg, confounding by indication),[9] and additional data need to be collected to define the relevance of AA as a specific risk factor.

The results of the study should be interpreted considering some limitations: the investigators have traced causes of death from medical records rather than from death certificates only in the patients' group. Moreover, disease severity was not evaluated in the population of patients with C1-INH-HAE. Data on mortality of patients with HAE with normal C1-INH were not available in this database.

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