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INVESTIGATIVE REPORT

Epidemiology of Non-hereditary Angioedema

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The prevalence of non-hereditary angioedema was investigated in a general population sample (*n* = 7,931) and in a sample of Danish patients (*n* = 7,433) tested for deficiency of functional complement C_1 esterase inhibitor protein (functional C_1 INH). The general population sample (44% response rate) reported a lifetime prevalence of 7.4% for angioedema. In both groups symptoms were most frequent in the lips, head, neck, eyes and tongue. In the C_1 INH test normal group angioedema was still active at the time of the study in 53% of the patients, and 36% reported symptoms in the throat, 23% in the abdominal area, 17% had diarrhoea, 11% had vomiting and 6% fainted during attacks. Non-hereditary angioedema has high lifetime prevalence and becomes chronic in approximately 50% of affected patients. Symptoms in the larynx and throat, as well as non-specific symptoms, such as dizziness and abdominal pain, were more frequent than previously reported. *Key words: angioedema; epidemiology; Quincke oedema; idiopathic angioedema.*

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Angioedema is characterized by localized swelling of sudden onset affecting the skin and/or mucous membranes (1). There are 2 major types of angioedema: the rare hereditary angioedema (HAE) and the more common non-hereditary angioedema (non-HAE). In only approximately 20–40% of cases does diagnostic work reveal the cause of non-HAE (2, 3). Good treatment options are available but the possibility of cure may be fairly uncertain (2, 4).

Non-HAE is typically a benign, self-limiting disease, but in some cases it can become a lifelong, troublesome disease. Angioedema lasting more than 6 weeks is defined as chronic angioedema (5, 6). International guidelines (5, 6) and reviews of urticaria (7) and angioedema (2, 4) describe the classical symptoms and specify the recommended diagnostic work-up and pharmacological treatment, but in most cases there are no clear answers to questions patients ask concerning disease prevalence, duration, intervals of attacks, cause and the risks of a fatality.

We analysed data collected in the Health2006 population study (8) to examine the prevalence of non-HAE angioedema. We also analysed data from patients tested for functional complement C_1 esterase inhibitor (C_1 INH), reasoning that, from this group, we could select a large subset of patients who had experienced episodes of angioedema. Using both datasets we describe the temporal and spatial patterns of non-HAE and the related mortality.

METHODS

The Health2006 population

Data concerning the general population were culled from the database of the Health2006 study, a random sample of the general population, aged 18–69 years, drawn from the "Det Centrale Personregister" (CPR; Central Person Register) and examined between June 2006 and June 2008. Each Danish citizen is assigned a CPR number, which serves as a personal identification number. The number indicates their date of birth and sex and links to additional data in the CPR office including the individual's vital status and current address.

Details of the Health2006 study have been published elsewhere (8). The Health2006 study was approved by the ethics committee of Copenhagen County (KA-20060011) and the Danish Data Protection Agency. Selection of participants is shown in Fig. 1.

Functional complement C_1 esterase inhibitor protein group

Between 28 March 1996 and 6 April 2005, only one laboratory in Denmark performed all analyses of functional C_1 INH. The laboratory used a Dade Behring calibrator based on a human normal plasma pool, with activity set to 100%. The laboratory participated in a double-blind quality control study of C_1 INH measurements (9). The results of laboratory analyses and the CPR number of all persons who had functional C_1 INH analysed during that period were obtained. This group of patients was designated the "C_1 INH group". The C_1 INH group was selected in 2007 from all patients having a functional C_1 INH determined from 1996–2005. The subset of patients in the C_1 INH group whose functional C_1 INH was $\geq 50\%$ was designated the "C_1 INH test normal group" (Table SI; available from http: //www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1389). Patients with incomplete results or without a CPR number were not included in the analysis.

Vital status data were checked through CPR records, and the National Board of Health provided death certificates upon request for any patients who died before January 1, 2006. We then sent the questionnaire to all individuals on the list who were alive in 2006 and had not indicated to the CPR registry that they did not want to be contacted for research purposes.

The C_1 INH study was approved by the Danish Data Protection Agency. Ethics board approval of surveys based on questionnaires is not required in Denmark.

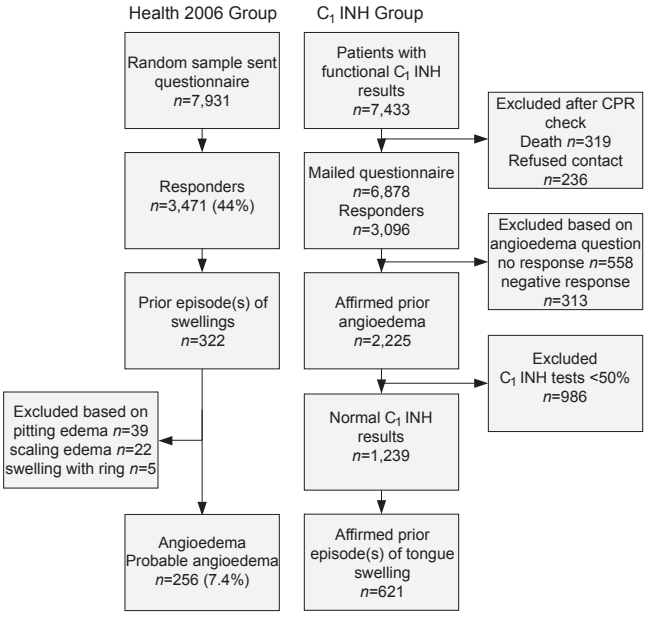

Fig. 1. Selection of patients for the general population group and the C_1 INH group.

Study questionnaires

A specific questionnaire for the C_1 INH group was developed, since to our knowledge no validated or standardized questionnaires on angioedema or urticaria were available. The questionnaire was developed based on qualitative interviews and symptoms presented in the literature using a systematic approach that included questions about symptoms from every organ system.

The C_1 INH questionnaire was initially tested in 11 patients with specialist-diagnosed angioedema. The questionnaire was then revised and posted to the C_1 INH group along with a cover letter introducing the study and explaining the nature and symptoms of angioedema and urticaria in non-technical language.

All participants in the Health2006 study answered a screening question on angioedema: "Have you ever had swellings of the lips, the tongue or the skin, which developed quickly and disappeared within a few days?" The participants who gave an affirmative answer to the screening question completed a more detailed questionnaire on angioedema (for details see Table I). The questionnaire used for the general population group was a shorter version of the C_1 INH questionnaire.

Statistical analyses

IBM-SPSS 19 and Microsoft Excel software were used for statistical analyses. Standardized mortality rate (SMR) was calculated by indirect age standardization separately for each sex using Danish mortality data in the relevant period obtained from Statistics Denmark. Confidence intervals (95% CI) were calculated by assuming a Poisson distribution of the number of deaths.

RESULTS

The Health2006 population consisted of the 3,471 individuals (44%) who responded to the study questionnaire (Fig. 1). A total of 322 of the 3,471 participants (10.1%) answered "yes" to the screening question on angioedema ("Have you ever had swellings of the lips, the tongue or the skin which developed quickly and disappeared after a few days?"). Thirty-nine participants also answered "yes" to the follow-up question on pitting oedema ("Would a pit in the swelling created by pressure, e.g. from a finger, persist for more than few seconds?"). From the remaining participants we excluded 22 who reported scaling of the swellings, and 5 who reported that the swelling was surrounded by a red ring, since angioedema is considered a non-pitting, non-scaling erythematous or skin-coloured oedema (2, 4). Thus, the angioedema group in the Health2006 population consisted of 256 subjects from the initial population of 3,471 (7.4%; 95% CI: 6.5–8.3).

Table I. *General population group: location, quality and self-reported causes of symptoms ranked by frequency (*n = *3,471)*

Characteristics	*n* (%)[a]
Prevalence	256 (7.4)
Location of symptoms	
Lips	95 (37.1)
Eyes	43 (16.8)
Head, arms, legs or body	40 (15.6)
Tongue	40 (15.6)
Other localization	35 (13.7)
Larynx	15 (5.9)
Genitalia	3 (1.2)
Quality of symptoms	
Red	100 (39.1)
Itching	90 (35.2)
Coloured like the other skin	36 (14.1)
Painful	37 (11.3)
Difficulties with breathing due to swelling of the airways	19 (7.4)
Cause of symptoms	
Food	91 (35.5)
Medication	25 (9.8)
Insect sting	19 (7.4)
Infection	17 (6.6)
Autoimmune disease	6 (2.3)
Coexisting symptoms	
Hives	91 (35.5)

[a]Total does not add up to 100% due to persons giving multiple responses.

Table I presents the qualitative characteristics and anatomical location of angioedema reported by subjects in a random sample of the general population. Patients suspected food, medications, insect sting and infection to be the primary triggers of angioedema episodes. A history of hives was reported by 124 of the 3,471 subjects (3.6%; 95% CI: 3.0–4.2) and by 91 of the 256 subjects (35.6%; 95% CI: 29.7–41.8) who responded affirmatively regarding angioedema episodes in the general Health2006 questionnaire.

Functional complement C_1 esterase inhibitor protein group

Over the 9-year period from 1996 to 2005, a single Danish laboratory performed 8,992 functional C_1 INH analyses. We excluded 24 events because a functional C_1 INH result was missing and 2 events because the CPR number was missing, leaving a complete dataset consisting of 8,966 measurements performed on 7,433 distinct patients. We then compared this patient list with a list from the CPR

office, and found that 319 patients had died and that 236 did not allow postal contact for research purposes. Thus, 6,878 patients met the inclusion/exclusion criteria and were sent a postal questionnaire (Fig. 1).

Of the 3,096 individuals (45.0%) who returned the questionnaire, 558 did not answer the question about a previous episode of angioedema. Of the remaining 2,538 who answered the question, 2,225 affirmed "having ever had angioedema" and 1,239 had a functional C_1 INH ≥50%. In the latter group, approximately half of the patients (652/1,239) reported still having angioedema swellings.

The temporal pattern of symptoms is shown in Table II. In 735 patients (735/1,239; 59.3%) all episodes together lasted for less than 4 weeks. A total of 203 patients (16.4%) reported no longer having angioedema, and 340 patients (27.5%) were unsure whether the angioedema had disappeared.

Table III presents the clinical symptoms of angioedema reported by the C_1 INH test normal group. Angioedema occurred after 11 years of age in most patients in the C_1 INH test normal group who reported having angioedema. Symptoms most frequently affected the lips, tongue, head and neck, eyes, arms and legs. Approximately one-fifth of respondents reported throat-related symptoms without a sensation of choking, and 292 (23.6%) reported feeling a choking sensation during an episode. Of the 292 who had experienced a choking sensation 198 (69.0%) had experienced hives ever and 125 (43.9%) had experienced a choking sensation and hives at the same time. The majority of respondents reported experiencing difficulties with breathing and itching of swollen tissue during attacks (Table III). Other relatively common symptoms included dizziness, abdominal pain and diarrhoea. In cases where a medical condition was identified as precipitating an attack, the conditions that were most frequently identified were sinusitis (15%), herpes infection (12%), connective tissue disease (10%) and cystitis (11%). Thirteen patients (2.5%) reported antihypertensive treatment as the cause of their swellings.

A general practitioner was reported to have identified angioedema in 11% of cases, a specialist in 27% and a practitioner of complementary medicine in 8%. The cause of angioedema was reported to be food and beverage (15%), psychological stress (11%), pollen or animals (11%), pressure (9%), heat (8%), cold (7%), food preservatives (7%), antibiotics (7%), sunlight (4%) and water (3%).

Symptom quality and frequency was analysed in patients who reported swelling of the tongue and who had functional C_1 INH ≥50% (n=621) (Tables SII and SIII; available from http: //www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1389). Fig. 2 shows the distribution of functional C_1 INH determined in serum from 7,400 distinct individuals.

The mortality analyses included all deaths (n=309) from 1996 to 2005 in patients with C1 INH ≥50% without lymphoma or myelofibrosis (n=9), leaving 300 deaths for the mortality analyses, but only 2 of the 9 patients had functional C_1 INH <50%.

The standardized mortality rate (SMR) was calculated by indirect age standardization comparing the 300

Table II. *C1 INH test normal group (C_1 INH test ≥50%). The temporal pattern of angioedema: debut, remittance and relapse in patients answering "yes" to the question: "Have you ever had swellings of the lips, the tongue or the skin which developed quickly and disappeared after a few days?"* (n = *1,239)*

	n (%)[a]
Have you had hives as explained below?	
Yes	825 (66.6)
No	211 (17.0)
Don't know	173 (14.0)
Have you ever had angioedema and hives at the same time?	
Yes	468 (37.8)
No	415 (33.5)
Don't know	335 (27.0)
Do you still suffer from angioedema?	
Yes	653 (52.7)
No	203 (16.4)
Don't know	340 (27.4)
Relapses with >5 years interval?	
1 time	295 (23.8)
2 times	113 (9.1)
3 times	91 (7.3)
4 times	47 (3.8)
≥5 times	464 (37.4)
For how long did the angioedema episodes last?	
1 week	567 (45.8)
1–2 weeks	126 (10.2)
3–4 weeks	42 (3.4)
1–2 months	29 (2.3)
2–3 months	23 (1.9)
>3 months	130 (10.5)
How many years has past since your first attack?	
15 years	309 (24.9)
14–10 years	259 (20.9)
9–5 years	432 (34.9)
4–3 years	185 (14.9)
<2 years	36 (2.9)
Maximum interval between attacks	
≥15 years	23 (1.9)
14–10 years	23 (1.9)
9–5 years	75 (6.1)
4–3 years	78 (6.3)
2 years	85 (6.9)
1 years	126 (10.2)
6 months	172 (13.9)
3 months	147 (11.9)
1 month	111 (9.0)
2 weeks	72 (5.8)
Episodes every week	143 (11.5)
Age at first attack	
<1 year	4 (0.3)
1–2 years	15 (1.2)
3–4 years	22 (1.8)
5–10 years	67 (5.4)
11–20 years	201 (16.2)
21–40 years	431 (34.8)
41–60 years	394 (31.8)
61–80	79 (6.4)
>80 years	3 (0.2)

[a]Total does not add up to 100% due to persons giving multiple responses.

Table III. *C_1 INH test normal group (C_1 INH test ≥50%): spatial pattern and quality of symptoms ranked after frequency in patients answering "yes" to the question: "Have you ever had swellings of the lips, the tongue or the skin which developed quickly and disappeared after a few days (*n*=1,239)?"*

	n (%)[a]
Location of symptoms	
Lips	864 (69.7)
Head and neck	753 (60.8)
Eyes	747 (60.3)
Tongue	621 (50.1)
Arms	566 (45.7)
Legs	544 (43.9)
Throat (larynx) without choking sensation	446 (36.0)
Thorax	300 (24.2)
Abdominal area	289 (23.3)
Genitalia	244 (19.7)
Throat (larynx) with choking sensation	201 (16.2)
Breasts	181 (14.6)
Symptoms during attacks	
Itching swellings	931 (75.1)
Difficulty breathing	628 (50.7)
Stinging or burning swellings	589 (47.5)
Dizzy	379 (30.6)
Choking sensation	292 (23.6)
Abdominal pain	267 (21.5)
Near fainting	213 (17.2)
Diarrhoea	208 (16.8)
Vomiting	130 (10.5)
Fainting	76 (6.1)

[a]Total does not add up to 100% due to persons giving multiple responses.

patients who died with the mortality in the Danish reference population in the relevant period and age groups. The SMR was significantly increased for both women (SMR = 1.63; 95% CI: 1.40–1.90) and men (SMR = 1.72; 95% CI: 1.45–2.03). In only 1 case (C_1 INH = 144%) did the death certificate list angioedema as the cause of death. According to this patient's general practitioner the patient was treated with an angiotensin-converting enzyme (ACE) inhibitor for hypertension, and the patient's hospital record indicated that the patient was known to suffer from swellings and allergy to fish (the angioedema began in a supermarket).

In 12 other cases the person was found dead, and cardiac arrest was reported as the cause of death. In 11 other cases angioedema could not be ruled out as the main cause of death. The remaining death certificates gave no indication of death by angioedema.

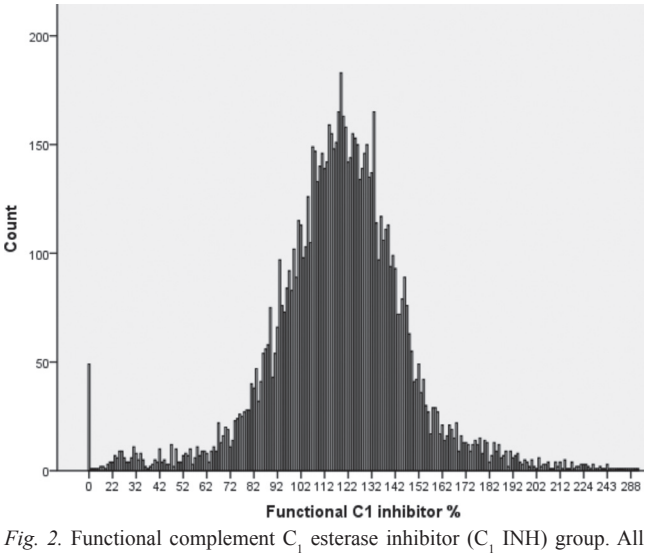

Fig. 2. Functional complement C_1 esterase inhibitor (C_1 INH) group. All measurements of functional C_1 INH performed in the period 1996–2005 in Denmark are shown (*n*=9,992). The figure includes results from patients with hereditary angioedema (HAE) and includes 7,433 unique patients. Functional C_1 results below the lower detection limit (<20%) are displayed as 0 activity (*n*=49).

DISCUSSION

The epidemiology of acute and chronic non-HAE in 2 large Danish populations is reported here. To our knowledge this is the first epidemiological study to focus on non-HAE. In contrast to previous data (10) and assumptions, the present report found angioedema to be more prevalent than urticaria in a general population, but distinguishing between angioedema and urticaria might be difficult, not only for patients but also for physicians.

The symptoms and spatial pattern of occurrence of symptoms were similar in the population study group and the C_1 INH test normal group. In both groups, the eyes, lips, tongue, face, and extremities were the areas most often affected (Tables I–III and SII). An important finding is that a substantial number of patients reported having experienced non-specific symptoms, such as dizziness (31%), abdominal pain (22%), diarrhoea (16%), near fainting (17%), vomiting (10%) and fainting (6%) simultaneously with their swellings. If these symptoms occur without the characteristic swellings of the tongue, the lips and eyes angioedema might not be recognized as the underlying cause.

The age- and sex-standardized mortality rates in the C_1 INH group were significantly increased compared with the mortality rates of the general population. Nevertheless, it was possible to identify only one case in the C_1 INH group where angioedema was reported as the primary cause of death (see Results).

Few epidemiological studies have been published on non-HAE. Vazquez et al. (11) found a lower prevalence of angioedema than we reported (5% vs. 7.4%), but their analysis excluded acute angioedema. Zuberbier et al. (12) reported a 19% prevalence of either urticaria or angioedema.

Approximately one-third of patients in the C_1 INH group reported symptoms located in the throat without a choking sensation and one-sixth in the C_1 INH group reported symptoms located in the throat with a choking sensation. One-fourth of patients in the C_1 INH test normal group reported having experienced choking-like episodes during angioedema attacks, challenging previous assumptions that the larynx is rarely involved in the non-

hereditary form of angioedema (2, 4). Notably, Zuberbier et al. (12) also found some involvement of upper airways, since "swelling in the oral cavity" was the symptom most frequently associated with chronic urticaria.

Functional C_1 INH showed a continuous unimodal distribution above the detection limit (Fig. 2), which precluded detection of a distinct threshold limit for functional C_1 INH to differentiate the 2 types of angioedema. However, 149 patients had reproducible functional C1 INH < 50%, compared with 82 Danish patients identified by Bygum (13) as having HAE. This difference gives some indication of the relative specificity of the C_1 INH test.

Strengths and limitations

The strength of our study is the large sample size. We have a random sample, consisting of the Health2006 population group, from which we could estimate the disease prevalence, and a symptomatic group, the C_1 INH test normal group, from which the temporal and spatial distribution of symptoms could be described with confidence.

The validity of an angioedema diagnosis based on self-reported symptoms remains uncertain, but the specific symptoms, when intermittent in nature, are characteristic of angioedema. Indeed, intermittent swelling of the tongue is not often observed in other conditions. Therefore, the similarity of the results (Tables SII and SIII) obtained from patients answering affirmatively to having had angioedema (n = 1,239) and from patients affirming having had swelling of the tongue (n = 621) indicates good specificity of our screening question. Most differential diagnoses (4), such as acute allergic dermatitis (which lasts longer and is scaling) or infectious facial cellulitis, are either rare or not easily confused with angioedema. Consequently, we doubt that misdiagnosis could have biased our results substantially.

On the other hand, the risk of underestimating the prevalence of non-HAE has also to be considered. Our screening question was designed to detect only those patients with classical symptoms, without considering patients with isolated non-specific symptoms, such as breathing difficulties, in the absence of classical symptoms. Thus, the prevalence of non-HAE might be even higher than our study indicates.

If C_1 INH measurements were performed only in chronic cases, then selection bias could have occurred. Selection of patients with more severe forms of angioedema might result in an overestimation of both the duration and severity of the disease. We consider overrepresentation of severe cases in the C_1 INH group unlikely, since half of the cases were reported as acute rather than chronic angioedema.

In conclusion, non-HAE angioedema is a common disease with a high lifetime prevalence of 7:100 compared with that of HAE (1.4:100,000) (10) and a slightly increased mortality. Non-HAE angioedema occurs in patients of all ages and becomes chronic in half of cases. An important finding was that the symptoms in the larynx and throat, as well as non-specific symptoms, such as dizziness and abdominal pain, were more frequent than previously reported. Angioedema should be considered in unexplained cases of dyspnoea, dizziness, fainting and gastrointestinal symptoms.

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