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Hereditary angioedema: do patients have a specific "digital fingerprint" in Danish registries?

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Abstract

Introduction: Hereditary angioedema (HAE) is a potentially life-threatening genetic disorder characterized by recurrent episodes of angioedema. From the onset of symptoms until diagnosis, patients often have several contacts with the healthcare system. It was hypothesized that a "digital fingerprint" of undiagnosed HAE patients could be identified in Danish registries.
Methods: This study compared patients with a control group of patients with a diagnosis of Quincke's edema (QE) or bee/wasp allergy because they could have phenotypic similarities.
Results: QE was the most common diagnosis code in the hospital sector among HAE patients before a specific diagnosis of HAE was established. HAE patients had been seen at the hospital on average once every other year before the diagnosis was established, and on average once during the year before the diagnosis was established. Many patients contacted a practicing dermatologist during the year before the diagnosis was established.
Conclusions: HAE patients had several hospital contacts due to swelling attacks during the years before their diagnosis was established, and half of them consulted a dermatologist. It was not possible to identify a specific "digital fingerprint" in Danish registries regarding specific procedures or diagnoses distinguishing them from the control group. It is therefore recommended that hospitalized patients with angioedema of unknown cause be screened for HAE.

Keywords: hereditary angioedema, patient journey, digital fingerprint, Denmark, rare disease

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Introduction

Orphan diseases are by definition rare, and patients suffering from rare diseases may remain undiagnosed for years and even die without an accurate diagnosis (1). The low prevalence of one to two per 10,000 persons, and the fact that many rare diseases are commonly characterized by a combination of unspecific symptoms, makes them challenging to diagnose (2). Computer learning and diagnostic algorithms could potentially aid in diagnosis and minimize clinician error (3). One of the most important factors related to diagnostic delay is the lack of suspicion of a rare disease by both patients and their physicians (4).

Hereditary angioedema (HAE) is a rare and potentially life-threatening genetic disorder characterized by recurrent episodes of angioedema (5–7). The attacks can occur in any part of the skin, airway, gastrointestinal tract, or genitourinary system, and they can be extremely painful. The disease can cause substantial pain and stress, and, due to the character of the symptoms, undiagnosed HAE can lead to unnecessary procedures and treatment of patients. For patients living with HAE, the burden of disease is significant (8–10). The earlier a correct diagnosis of HAE is given, the sooner patients can relieve the burden of disease by receiving specific therapy and avoiding unnecessary contacts and ineffective therapies in the healthcare system. Despite advances in establishing international guidelines for correct diagnosis and management, there is still a diagnostic delay for patients with HAE. This is partly because the disease remains unknown to many physicians, but also because the disease symptoms can imitate other disorders with swelling of skin or mucosa as well as abdominal pain. In some parts of the world, there is also limited access to recommended diagnostic tests such as complement C1-inhibitor measurement and molecular genetic testing (9). In a Danish study published in 2009, the mean diagnostic delay was 16.3 years (11). However, this improved dramatically to a mean diagnostic delay of 1.6 years from 2009 to 2013, possibly due to increased awareness and collaborative work between the patient organization and the National HAE Center (8, 12). In the years from the first symptoms until diagnosis, patients often had several contacts with the healthcare system, being treated for presumed allergy, urticaria, cellulitis, or acute abdomen, such as appendicitis. Denmark has a long tradition of using registries as invaluable data sources for administrative (e.g., reimbursement), quality surveillance, and research purposes (13–15). As an example, the Danish National Patient Register established in 1976 includes information on all patients in Danish hospitals. Every time a patient has contact with the Danish hospital service as a part of examinations, treatments, or operations, several registrations are collected and linked to the specific contact and patient (13). Information on outpatients is available from 1995 onward.

The term *Quincke's edema* is an old and imprecise term that is widely used for angioedema, especially in Danish medical journals, in registries, and as a diagnosis code in Danish coding systems. For this reason, the term is used in this article, although optimally it should be avoided in the future.

This study hypothesizes that a special "digital fingerprint" of undiagnosed HAE patients can be identified in Danish registries, and that this can be used to track undiagnosed patients in the future.

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Methods

Study design and patients

A retrospective register-based study was performed using the Danish National Patient Register, the National Health Insurance Service Register, and the Danish Population Register (13–15). These data sources permitted a population-based study covering all inhabitants in Denmark (approximately 5.9 million). The study period for a given patient was from 2000 to 2018. Patients were identified by the International Classification of Diseases, 10th Revision (ICD-10) code DD841A, with a contact at the National HAE Center checking that all Danish HAE patients and incident cases had no prior record of contact with a diagnosis of HAE (inpatient since 1977 and outpatient since 1995). A control group was created with the diagnosis codes DT783 Quincke's edema, DT634A Bee sting, and DT634B Wasp sting. The purpose of the choice of the control group was to compare HAE patients with patients that could present with a similar clinical picture and to determine whether the HAE patients differed from the control group.

Study procedure

An explorative approach was applied to examine different variables, including personal identification, diagnosis codes, procedure codes, and hospital departments. We used the term *observation* to illustrate the patient's contacts through the healthcare system, which include all registrations with a diagnosis, procedure, treatment, operation, or examination code within the primary and secondary care sector.

Data extraction was carried out by Statistics Denmark, and the data processing was performed with the statistical software package STATA. If a patient occurred in both populations, he or she would be excluded from the control group and be counted as an HAE patient.

Statistical analysis

The analysis was carried out by identifying incident HAE patients based on a new diagnosis code of DD841A and a contact at the National HAE Center checking all Danish HAE patients. Once identified, we investigated the frequencies of diagnoses and procedures in the study period from 2000 to 2018 for the HAE patients and the control group. All diagnoses, procedures, and contacts within the primary and secondary care sector within the defined study period were counted to potentially find unexpected pathways. We also investigated whether certain diagnoses, procedures, and visits were dominant during the 5 years until the HAE diagnosis. Descriptive statistics were applied.

Results

Table 1 shows an overview of the results. The preliminary results yielded 621 potential patients with a new HAE diagnosis; however, only 133 patients (70 males and 63 females) were confirmed based on registration at the National HAE Center. Forty-one of these (31%) were under 20 years old. A total of 30,485 patients (15,158 males and 15,327 females) were included in the control group based on a diagnosis code of Quincke's edema, bee sting, or wasp sting. Of these, 3,838 (12%) were under 20 years old. Demographic data are presented in Table 2. Among HAE patients, the five most common contact diagnoses at the hospital before HAE was established were

Table 2 | Overview of the demographic data and distribution of diagnoses for the hereditary angioedema (HAE) patient population and the control group.

Population characteristics	HAE patients, *n* (%) *N* = 133	Control group, *n* (%) *N* = 30,485
Diagnoses	HAE: 133 (100)	Quincke's edema: 16,462 (54) Bee sting: 4,267 (14) Wasp sting: 9,756 (32)
Age group		
0	9 (7)	132 (< 1)
1–5	10 (8)	974 (3)
6–10	7 (5)	806 (3)
11–19	15 (11)	1,918 (6)
20–29	15 (11)	3,158 (10)
30–39	17 (13)	3,669 (12)
40–49	17 (13)	4,615 (15)
50–59	18 (14)	5,188 (17)
≥ 60	25 (19)	10,025 (33)
Sex		
Male	70 (53)	15,158 (50)
Female	63 (47)	15,327 (50)

Table 1 | Overview of the number of observations in the primary healthcare sector, and the five most common hospitals, hospital departments, and primary healthcare providers for the hereditary angioedema (HAE) population and control group. Data were obtained from 2000 to 2018 and cover a period of the last 5 years until a diagnosis of HAE was established.

Short description	HAE patients (*n*) *N* = 133	Control group (*n*) *N* = 30,485
Average observations at hospital during last 5 years before diagnosis	6	6
Five most common contact diagnoses at hospital before diagnosis	1. Quincke's edema (204) 2. Radiological examination (179) 3. Unspecified disorder (83) 4. Lymphoma (52) 5. Breast cancer (30)	1. Radiological examination (52,551) 2. Unspecified disorder (14,076) 3. Allergy unspecified (2,760) 4. Suspicion of other disease or condition (7,691) 5. Hypertension (7,152)
Most commonly consulted departments before diagnosis established	1. Orthopedics (356) 2. Gynecology and obstetrics (314) 3. Radiology (153) 4. Internal medicine (138) 5. General surgery (74)	1. Orthopedics (101,126) 2. Radiology (54,194) 3. Gynecology and obstetrics (53,174) 4. General surgery (38,140) 5. Internal medicine (37,583)
Top five providers at primary healthcare sector before diagnosis established	1. General practitioners (6,666) 2. Dentists (1,384) 3. Physiotherapists (865) 4. Phlebotomists (535) 5. Ear, nose, and throat specialists (230)	1. General practitioners (1,938,784) 2. Dentists (431,168) 3. Phlebotomists (349,506) 4. Physiotherapists (216,833) 5. Reimbursed physiotherapists (132,629)
Observations in primary healthcare sector during last 5 years before diagnosis	20	26

Quincke's edema, radiological examination, unspecified disorder, lymphoma, and breast cancer. The HAE population and the control group both had a mean of six hospital contacts during the last 5 years before diagnosis. The five most common contact diagnoses at the hospital in the control group before diagnosis were radiological examination, unspecified disorder, allergy unspecified, suspicion of another disease or condition, and hypertension. The HAE population most commonly consulted the following departments (ordered by frequency) before the diagnosis: orthopedics, gynecology and obstetrics, radiology, internal medicine, and general surgery. The control group most commonly consulted the following departments before the diagnosis: orthopedics, radiology, gynecology and obstetrics, internal medicine, and general surgery. Among HAE patients, the top five providers in the primary healthcare sector before diagnoses were general practitioners, dentists, physiotherapists, phlebotomists, and ear, nose, and throat specialists. In addition, it was observed that pediatricians ranked as the sixth most common healthcare provider. In the control group, the top five providers in primary healthcare before diagnosis were general practitioners, physiotherapists (both reimbursed and self-payment consultations), phlebotomists, and dentists.

Discussion

In this retrospective register-based study, the preliminary data showed a total of 621 potential HAE patients in the study period, which was quite surprising based on a prevalence rate of 1:71,000 in Denmark (12). However, from former register-based studies in Denmark it is known that the positive predictive value of diagnoses varies between 15% and 100% and, especially for rare disorders, may be low (16–20). Diagnosis coding is performed manually by doctors or secretaries, which makes the system susceptible to miscoding. Because all HAE patients in Denmark are presumed to be affiliated with the National HAE Center at Odense University Hospital, where medication is dispensed, only patients registered at this department were included, resulting in a total of 133 patients. Based on a population of 5.9 million, this corresponds to an incidence rate of 1:44,000. This number includes HAE with normal and low complement C1-inhibitor and acquired complement C1-inhibitor deficiency (AAE) because the coding system does not make it possible to distinguish between the different subtypes (6, 12).

A control group of patients with acute and potentially life-threatening attacks was chosen to observe specific healthcare resource uses in HAE populations. The HAE patients were comparable to the control group regarding the number of observations at the hospital and in primary care before diagnosis. However, the HAE patients had more hospital contacts due to Quincke's edema, although the control group mostly consisted of patients with a diagnosis of Quincke's edema (54%). HAE patients had been seen at the hospital due to swelling attacks on average once every other year before the diagnosis was established, and on average once during the year before the diagnosis was established (Table 3). This means that HAE patients attend the hospital more frequently compared to the control group. This could be a clue to the diagnosis, and healthcare staff are advised to be especially aware of returning patients ("frequent flyers") with Quincke's edema. Because no specific pattern of contacts could be elucidated, it is recommended that all patients with a diagnosis of Quincke's edema of unknown cause attending a hospital should be screened for HAE (6, 21). This is apparently not the case because only around 1,000 analyses of functional complement C1-inhibtor are performed yearly (22). Clinicians should be aware that some patients develop a transient erythematous prodromal rash (erythema marginatum) prior to an angioedema attack that could be misinterpreted as urticaria by non-dermatologists, and that this could potentially lead to HAE not being suspected.

Distinctive treatment pathways were also sought for HAE patients, but it was not possible to find any clues in the HAE population compared to the control group. Surprisingly, the top provider for HAE patients was orthopedics. This could be because most emergency departments in Denmark are affiliated with orthopedic supervision.

Another interesting finding was contact with a practicing dermatologist during the year before diagnosis of HAE. In fact, 57 contacts were registered for 119 patients (Table 4), which is highly significant. Individual patients could have multiple contacts. This suggests that during their journey HAE patients consult a practicing dermatologist, and that this paves the way for a diagnosis within 1 year. It is especially interesting because no dermatology contacts were noticed 2 to 5 years before diagnosis, and no dermatology contacts were noticed in the control group. In Denmark, the National HAE Center is based at the Department of Dermatology and Allergy Center in Odense. All upcoming specialists are taught about this condition, and a guideline for handling suspected HAE is available from the Danish Dermatological Society. This could explain why visiting a dermatologist could lead to the diagnosis. Finally, a significant age difference was noticed between the HAE population and the control group. Greater proportions of children and young adults under 20 were observed in the HAE population (31% vs. 12.4%), whereas a higher percentage of individuals 50 and above were present in the control group (50% vs. 33%). This could be because only incident cases were included in the HAE population and not in the control group. In addition, it

Table 3 | Overview of the five most common contacts at the hospital 5 years before diagnosis of hereditary angioedema (HAE).

Condition	Observations (*n*) by years before				
	1	2	3	4	5
	N = 89	*N* = 60	*N* = 61	*N* = 51	*N* = 53
Pregnancy					13
Skin cancer, unspecified				11	
Breast cancer, unspecified	30				
Complement system defect					16
Extranodal marginal B-cell lymphoma		12			
Fibromyoma, unspecified				10	
Radiological examination	73	33	29	22	22
Mantle cell lymphoma	40				
Suspicion of another disease or condition		10	23		
Unspecified disorder	27	19	16	10	11
Periarthrosis humeroscapularis			12		
Quincke's edema	92	29	23	26	34

Table 4 | Overview of the top five providers in the primary healthcare sector 5 years before diagnosis of hereditary angioedema (HAE).

Provider	Observations (*n*) by years before				
	1	2	3	4	5
	N = 119	*N* = 115	*N* = 110	*N* = 108	*N* = 100
General practitioners	1,463	1,513	1,265	1,346	1,079
Dermatologists	57				
Physiotherapists	125	69	163	185	323
Phlebotomists	191	121	133	90	
Pediatrics					50
Dentists	304	249	280	279	272
Ear, nose, and throat specialists		47	63	69	51

was observed that pediatricians ranked as the sixth most common healthcare provider. Pediatricians are often the first physicians to examine children with HAE before diagnosis, but it is estimated that the diagnosis of HAE is made by pediatricians in only 3% of cases (23). It is therefore important that pediatricians be familiar with HAE because half the patients develop symptoms before the age of 10 (24). Evidently, children with HAE still experience a considerable diagnostic delay with multiple doctor visits and many years before confirmation of the diagnosis (25). The burden of disease for children with HAE includes a negative impact on both school attendance and performance, and this could prevent future career and education opportunities (23). Recent publications have focused on diagnosing HAE in children and adolescents, and it is recommended that physicians screen all children with a high suspicion of HAE, regardless of family history (23, 26, 27).

The strength of this study is the use of well-established high-quality nationwide registries, which increases the likelihood of reliable information (18, 19). Limitations include the fact that National Patient Register data are collected for administrative purposes rather than research. For this reason, it cannot be ruled out that there are challenges with the validity of the registrations. This is exemplified in the preliminary results identifying 621 patients with HAE even though the literature estimates around 100 patients in Denmark (12). Fortunately, the follow-up and treatment of HAE patients in Denmark are centralized at the National HAE Center, and therefore it was possible to identify true HAE patients based on later affiliation with that department. Some HAE patients not affiliated with the National HAE Center may potentially have been missed, although it is unlikely that a patient with verified hereditary angioedema has not been prescribed medication or is not receiving it. The patient organization will also refer HAE patients to the National HAE Center, and all laboratory results from Danish laboratories regarding reduced and/or dysfunctional C1-inhibitor will come with a recommendation about referring the patient to the National HAE Center, which would minimize the risk of missing HAE patients. Although a total of 133 patients in the HAE population is a relatively fair sample size, the size could be a potential limitation of the study because it is challenging to determine whether the results are related to HAE or whether they are only accidental findings. On a more technical note, the small sample size may have limited the level of detail that could be extracted from the research database because each cell value that was extracted had to have at least five observations. This could have been solved by grouping observations into more high-level categories, but with the risk of losing detail. Unfortunately, the level of detail in the diagnosis codes did not make it possible to identify the different subtypes of HAE. In addition, the terms used in the ICD-10 diagnosis code to encompass these patients could be confusing because *angioneurotic* and *Quincke's edema* are older terms, which means some patients may not be properly classified. Moreover, using the term *Quincke's edema* could have limited the study by not including all spontaneous mast cell angioedema with other locations, but the decision on the control group was made because in clinical everyday life these are patient groups with similarities. The study did not control for age differences of the observations in primary and secondary care, although the control group had a larger proportion of elderly people. Because contact with the healthcare sector increases with age, it cannot be excluded that elderly HAE patients had more observations in primary care and hospitals.

Conclusions

HAE patients had several hospital contacts due to swelling attacks during the years before the diagnosis was established. Because they could not be distinguished from a control group of patients with Quincke's edema or bee/wasp sting, it is recommended to screen patients for HAE with a blood test when they are hospitalized with a diagnosis of angioedema of unknown cause. Furthermore, many HAE patients had contact with a practicing dermatologist during the year before a diagnosis of HAE was established, suggesting that an examination by a dermatologist could pave the way for a diagnosis of HAE. Finally, because HAE patients were significantly younger when first presenting with symptoms compared to the control group, it is important that pediatricians be familiar with HAE.

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References

1. Marwaha S, Knowles JW, Ashley EA. A guide for the diagnosis of rare and undiagnosed disease: beyond the exome. Genome Med. 2022;14:23.
2. State of the art of rare disease. Activities in EU member states and other European counties. Denmark report [Internet]. [Cited 2023 Oct 31]. Available from: http://www.rd-action.eu/wp-content/uploads/2017/10/Denmark-Report-06.10.2017.pdf.
3. Evans WR. Dare to think rare: diagnostic delay and rare diseases. Br J Gen Pract. 2018;68:224–5.
4. Isono M, Kokado M, Kato K. Why does it take so long for rare disease patients to get an accurate diagnosis? A qualitative investigation of patient experiences of hereditary angioedema. PLoS One. 2022;17:e0265847.
5. Busse PJ, Christiansen SC. Hereditary angioedema. N Engl J Med. 2020;382:1136–48.
6. Maurer M, Magerl M, Betschel S, Aberer W, Ansotegui IJ, Aygören-Pürsün E, et al. The international WAO/EAACI guideline for the management of hereditary angioedema—the 2021 revision and update. Allergy. 2022;77:1961–90.
7. Bork K, Siedlecki K, Bosch S, Schopf RE, Kreuz W. Asphyxiation by laryngeal edema in patients with hereditary angioedema. Mayo Clin Proc. 2000;75: 349–54.
8. Bygum A. Hereditary angio-oedema for dermatologists. Dermatology. 2019;235:263–75.
9. Longhurst H, Bygum A. The humanistic, societal, and pharmaco-economic burden of angioedema. Clin Rev Allergy Immunol. 2016;51:230–9.
10. Mendivil J, Murphy R, de la Cruz M, Janssen E, Balle Boysen H, Jain G, et al. Clinical characteristics and burden of illness in patients with hereditary angioedema: findings from a multinational patient survey. Orphanet J Rare Dis. 2021;16:94.