

Variability of prodromal signs and symptoms associated with hereditary angioedema attacks: A literature review

John G. Kemp, D.O., and Timothy J. Craig, D.O.

ABSTRACT

Hereditary angioedema (HAE) is a rare disease caused by deficiency in the production or function of C1 inhibitor. It predisposes individuals to paroxysmal acute attacks causing painful, debilitating, disfiguring, and life-threatening angioedema. Prodromes occurring hours to days before attacks have been described in the literature; however, their significance as predictive signals of impending attacks is uncertain. Given the morbidity and mortality associated with HAE attacks and the increasing availability of therapeutic products for their treatment, identifying prodromes that accurately predict the onset of attacks could provide the basis for the development of a validated instrument to identify the onset of such attacks requiring abortive therapeutic intervention before the development of clinically significant angioedema. The aim of this study was to review the literature to identify the prodromes reported to occur with HAE attacks. A literature review of English language journal articles was performed using search terms hereditary angioedema, HAE, angioneurotic edema, prodrome, signs, and symptoms. Nineteen original English language articles that included both case reports and studies describing prodromes associated with HAE attacks were obtained. Our review indicates that there is significant variability in the expression, manifestation, prevalence, timing, and predictive reliability of the prodromes that have been described. There is considerable variability of the prodromal manifestations that may occur before or during HAE attacks. We have not found any evidence that their sensitivity and specificity for accurately predicting such attacks has been studied.

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Key words: Erythema marginatum, fatigue, gastrointestinal, HAE, hereditary angioedema, prodromal symptoms, rash, reticulate rash, treatment

Hereditary angioedema (HAE) is an autosomal-dominant inherited disease with an estimated prevalence between 1:10,000 and 1:50,000 in the general population.¹ It is caused by a deficiency in the plasma level of the serine protease inhibitor, C1 esterase inhibitor (C1-INH), the gene for which has been mapped to chromosome 11 (p11.2–q13).² This deficiency occurs because of either a decreased level of production of C1-INH (HAE type I) or as a result of the production of dysfunctional C1-INH protein (HAE

type II).³ C1-INH is involved in the regulation of vascular permeability by suppressing contact system activation. A deficiency in C1-INH caused by HAE predisposes an individual to an inappropriate activation of the contact system resulting in an increased release of bradykinin, which is believed to be the primary mediator involved in the recurrent acute episodes of angioedema.³ These acute episodes of angioedema occur paroxysmally and usually last for 3–5 days. Acute attacks often follow triggers such as trauma, infections, stress, dental work, or surgery, but more often occur spontaneously. They cause significant morbidity and predispose patients to an increased risk of mortality. The angioedema may occur in differing degrees of severity without pitting or pruritus and it is often localized to one or several areas of the body including the extremities, genitalia, face, oropharynx and tongue, laryngeal tissues, and visceral organs.⁴ The severity of the swelling can cause significant physical impairments, deformities, and pain when localized to the extremities, face, or genitalia. Visceral attacks of angioedema are also quite painful and may cause nausea, vomiting, diarrhea, and abdominal distension that can

From the Department of Medicine, Section of Allergy, Asthma, and Immunology, Penn State University, College of Medicine, Hershey, Pennsylvania

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Address correspondence and reprint requests to Timothy Craig, D.O., Department of Medicine, Section of Allergy, Asthma, and Immunology, Penn State University, College of Medicine, 500 University Drive, H041, Hershey, PA 17033

E-mail address: tcraig@psu.edu; alternative: tcraigpsu@yahoo.com

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also be very debilitating. Laryngeal episodes of angioedema are uncommon; however, more than one-half of HAE patients may experience such an attack during their lives, which places them at an increased risk of asphyxiation and death caused by laryngeal swelling.^{5,6}

For many years there have been C1-INH products available outside of the United States for the treatment of HAE and recently nanofiltered C1-esterase inhibitor (Viropharma, Exton, PA) has become the first C1-INH product to be approved by the Food and Drug Administration (FDA) as a prophylactic agent that may also effectively alleviate episodes of acute angioedema in this group of patients in the United States. More recently, ecallantide (Dyax, Lexington, MA) received a positive review by the FDA Advisory Panel and is awaiting a final decision for approval by the FDA for treatment of acute HAE attacks. There are at least three additional therapeutic agents that have either completed or are completing phase 3 studies that also appear to be effective in relieving the symptoms of acute attacks. With these recent advances, hope is becoming a reality that effective therapeutic agents are becoming available to treat patients with acute attacks of HAE in the United States.^{7,8} In light of the potential availability of such effective therapeutic agents to treat acute HAE attacks and given the significant morbidity and risk for mortality associated with such episodes, consideration should be given to development of the most effective diagnostic evaluation techniques that will yield the earliest possible detection of the onset of an HAE attack so that efficacious and abortive treatment can be initiated.

Prodromal signs and symptoms of HAE have been described in the literature for more than a 100 years. They may provide important predictive and diagnostic clues to the imminent development of an HAE attack signaling the need for immediate and definitive therapeutic intervention. The purpose of this study was to review the literature to identify the prodromes of acute HAE attacks that have been reported and to evaluate their potential value as prognostic indicators in heralding an acute attack of HAE.

METHODS

A literature review was performed using the Ovid Medline database (1950-July 2007) with the search terms hereditary angioedema, HAE, angioneurotic edema, prodrome, signs, and symptoms. Relevant English language journal articles were identified and reviewed for reports and information pertaining to prodromes associated with HAE. Bibliographies of the selected journal articles were also reviewed for additional pertinent articles that were also reviewed. All of the articles that we were able to identify and obtain

that had reports and information pertaining to the prodromes of HAE were included in Tables 1 and 2, which display the results of our literature review.

RESULTS

The Medline search using the search terms hereditary angioedema, HAE, angioneurotic edema, prodrome, signs, and symptoms and subsequent bibliography reviews yielded 19 original English language articles that included both case reports and studies that identified and described prodromes associated with HAE attacks. From those articles and data we designed two tables to more clearly evaluate and display the prodromes that have been reported. Table 1 lists the identified articles with the type of report and number of patients or subjects studied or described. It demonstrates the broad spectrum of reports and populations from which descriptions of prodromes associated with HAE attacks have emerged. Table 2 identifies the number of subjects that experienced specific types of prodromes in each of the 19 included articles. This table displays the significant variability in the expression, manifestation, prevalence, and predictive reliability of the prodromes that have been studied and described.

DISCUSSION

The results of our review of the literature reveal that there have been many reports and several studies describing prodromal signs and symptoms that occur before HAE attacks. Our results and the body of literature that we reviewed also indicate that there is significant variability in the predicative reliability, manifestation, timing, and reproducibility with which such prodromes occur. To organize our results and for the purpose of this review, we have categorized the various prodromes by their clinical manifestations as follows.

Prodromal Skin Manifestations

Skin manifestations of prodromes have been reported in 13/19 of the articles we identified and appear to be the most frequent to be described in the literature. They include various forms of rashes, erythema marginatum (EM), or EM-like eruptions, erythema, and mottling. Osler, in his description of one patient, noted a "slight redness" of the body part that would precede the swelling; however, he also observed that the redness would not always occur before an attack. He also described "red spots" and "irregular lines of redness" that would often occur and last 1–4 days without any related swelling during that period.⁹ Spaulding described a nonpruritic exanthem of "red rings" that may have been slightly raised that "may occur" the day before the onset of swelling in one of the two subjects he reported.¹⁰ Erythema multiforme "characterized by

Table 1 Articles and studies that identify prodromes associated with hereditary angioedema

Article No.	No. and Description of Subjects Reported
1. Osler W. (1888) ⁹	Two cases reported
2a. Crowder and Crowder (1917) ²³	One case reported
2b. Crowder and Crowder (1917) ²³	Excerpts of notes of a physician's experiences, J.R. Hinkle, who cared for members of a kindred of 4–5 families over 30 yr
3. Dunlap (1929) ²⁴	One case reported
4. Spaulding (1955) ¹⁰	Two cases reported
5. Cohen (1961) ¹¹	One case reported
6. Landerman (1962) ²⁵	One case reported
7. Donaldson and Rosen ¹²	Report describing observations of 47 affected members of 12 families with HAE
8. Hyman <i>et al.</i> (1967) ¹³	One case reported
9. Dennehy (1970) ²⁷	One case reported
10. Beck <i>et al.</i> (1973) ¹⁴	Four cases reported
11. Starr and Brasher (1974) ¹⁵	Two families with HAE with a combined number of 13 subjects evaluated
12. Frank <i>et al.</i> (1976) ¹⁶	Report on the clinical characteristics of 30 patients with HAE
13. Ohela (1977) ²⁶	Seven families with a combined number of 27 subjects with HAE studied
14. Williamson (1979) ¹⁷	Four generations of a large family with HAE described and personal communication with Warin and Staughton regarding two patients
15. Atkinson (1979) ¹⁸	Review based on Beck 1973, Frank 1976, and the authors experience with patients in several large families and those observed at NIH
16. Cicardi <i>et al.</i> (1982) ⁵⁵	Thirty-one families with a combined number of 104 HAE patients studied
17. Nielsen <i>et al.</i> (1996) ¹⁹	Study including clinical manifestations in 33 HAE patients from a kindred of 63
18. Farkas <i>et al.</i> (2001) ²⁰	Retrospective analysis of skin abnormalities accompanying attacks in 69 HAE patients studied
19. Yucelten and Kus (2006) ²²	One case reported

HAE = hereditary angioedema.

serpiginous erythematous welts" most often on the face was reported to occur in association with many of the attacks experienced by a 39-year-old woman in a case report by Cohen. He did not specify whether the eruptions would occur before or during an HAE attack.¹¹ Alternatively, diffuse mottling or "a narrow band of erythema" demarcating an area of pallor that would subsequently swell was noted to occur in several of the 47 members of the 12 families with HAE reported by Donaldson and Rosen.¹² Hyman *et al.* also described a variation of a similar prodromal eruption in a 33-year-old man who would develop "faint erythematous nonpruritic macules, first on the chest, with subsequent spread to the arms or back, in an annular or reticular pattern."¹³ An "erythema marginatum-like skin rash" was also observed to be associated with skin swelling attacks in one of four cases reported by Beck *et al.*; however, whether the rashes were prodromal or occurred simultaneously was not specified.¹⁴ The variability of such skin manifestations in their expression,

occurrence, and association with acute HAE attacks as described in those earlier reports were then highlighted by Starr and Brasher in their study of two families with HAE. Their study revealed that ~50% of their cohort who had HAE would develop EM before the onset of angioedema. They emphasized, however, that the rash would not occur before every attack and in one subject, the rash would occur at times even in the absence of a subsequent attack. They also noted that the angioedema would not necessarily occur at the site of the prodromal rash.¹⁵

Subsequent studies and case reports confirmed the observations made in those earlier articles, that skin manifestations do occur both before and during HAE attacks with significant variability in appearance and predictive reliability. This was observed by Frank *et al.* in their study of 30 HAE patients of which 26% ($n = 28$) were found to sometimes have a nonpruritic rash that occurred either before or with the angioedema. They noted that the rash also occurred at times indepen-

Table 2 Number of subjects reported to have experienced specific types of prodromes in each of the 19 articles reviewed

Article No. (per Table 1)	1	2a	2b	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Prodrome																				
Skin manifestations: 1/2 rash/EM or EM-like eruption/erythema/mottling	1/2	1/1	NS	1/1	1/1	1/1	1/1	NS	1/1	1/4	8/13	26% N = 28	NS	25% (NS)	12/24	29/39	1/1			
Paresthesias: 2/2 1/1 NS 1/1 itching/tingling/warmth/burning/pain/numbness/tightness	2/2	1/1	NS	1/1	1/1	5/20	1/1	5/20	1/4	1/4	NS/ N = 30	1/27	NS	15/21						
Fatigue and malaise	1/2	1/1	NS	1/1	1/1	1/1	1/1	1/1	1/1	1/4	5/27	2/27	NS	59/104	NS					
Change in affect or energy:																				
depression/anxiety/irritability/increased energy/"discomfort"	1/2	1/1	NS	1/1	1/1	1/1	1/1	1/1	1/1	1/1	2/4									
Gastrointestinal and fluid shift	1/2	1/1	NS	1/1	1/1	1/1	1/1	1/1	1/1	1/1	2/4									
manifestations:																				
anorexia/nausea/indigestion/nervous stomach/bloated and gassy/thirst/hunger																				

EM = *erythema marginatum*; NS = not specified; N = number.

dently of an attack.¹⁶ Reticulate nonpruritic erythema that could be diffuse in distribution, lasting 1–4 days before an attack was found by Williamson to be a common prodrome shared by four generations of a family with HAE. This eruption was, however, noted to occur at times without any subsequent swelling and, conversely, attacks would also occur without the prodromal rash.¹⁷ Similarly, “a non-descript, transient, erythematous, non-pruritic rash suggestive of erythema marginatum” that would erupt either before or during an HAE attack was described by Atkinson who estimated this to occur in 25% of HAE patients with whom he had experience or were included in his review.¹⁸

Several of the most recent articles published have yielded results that also support those findings that have previously been reported in the literature. Nielson *et al.* studied 33 members of a family with HAE and found 50% (12/24) to have reported a prodromal rash at times described as nonpruritic “iris-like red and slightly elevated circles in the skin” that occurred either before or during attacks and lasting <1 day. An unspecified number of 71% (15/21) of the subjects studied reported a prodrome that may have included a rash occurring 1–4 hours before an attack.¹⁹ In a retrospective analysis of the medical records of 69 HAE patients, Farkas *et al.* reported that EM had been observed in 29 of those patients. They reported it would always occur before the onset of an attack, last for 24–48 hours, and resolve with the resolution of the angioedema. They also noted that the EM occurred either before or during abdominal attacks in 11 of the patients.²⁰ Recently, Starr *et al.* further studied four members of the family previously described in 1974 and highlighted their findings that all four subjects had EM often occur before or with attacks of angioedema and that the EM would continue to recur with the same frequency in two of the patients treated with danazol despite the decrease in frequency of HAE attacks.²¹ Conversely, Yucelten and Kus recently reported a case in which an HAE patient presented with angioedema and a “reticulate, serpentine, macular erythema on the trunk” that did not recur with subsequent episodes of angioedema once the patient was on a danazol treatment regimen.²²

Prodromal Paresthesias

Our review revealed that various paresthesias including itching, tingling, warmth, burning, pain, numbness, and tightness have also been frequently described as prodromal symptoms before HAE attacks. They were described in 10/19 of the references we reviewed, the earliest of which was published in 1888 by Osler who reported two cases of patients with HAE. The first patient would experience prodromal itching and a sensation of heat. The second patient experi-

enced prodromal itching that occurred only sometimes before attacks.⁹ Crowder and Crowder also reported their experience with an HAE patient who described a prodromal sensation of tingling, burning, or, rarely, pain shortly before an attack.²³ They also published excerpts of the notes of a physician, J.R. Hinkle, who cared for several generations of a family with HAE. Within those excerpts, it was noted, “the swelling usually begins, or rather the first warning of the approach is in a small stinging sensation in the part attacked.” The sensation of “tingling over a small area” occurring within hours before the onset of angioedema at the same site was also described by Dunlap and Lemon in a case report of an HAE patient.²⁴ Landerman also reported a case of an HAE patient who would typically experience a prodromal numb sensation in an extremity for 2–3 hours before the onset of its swelling.²⁵ These early reports described several prodromal paresthesias that showed variability in both manifestation and reliability as predictive symptoms.

Several subsequent studies have also resulted in similar findings of variability in these prodromes. Donaldson found that 5 of the 20 HAE patients interviewed had sometimes experienced itching before the onset of angioedema with one subject having experienced itching that worsened with the swelling.¹² One of four HAE patients reported by Beck *et al.* had prodromes of a sense of tightness and numbness occur in the extremity that would then swell.¹⁴ Similarly, based on a relatively large cohort of 30 HAE patients, Frank *et al.* found that a prodromal tingling or tightness would often be reported by patients to occur at the site of subsequent swelling 30 minutes to several hours and, infrequently, up to 12–24 hours before the onset of angioedema.¹⁶ Ohela, who also reported on a similarly large cohort of 27 HAE patients found that only 1 of the 27 had, on the day before an attack, a prodromal sensation of pain in the area of subsequent swelling.²⁶ Atkinson, based on his review and extensive clinical experience with HAE patients, wrote that “the patient often notices a peculiar tingling or twitching in the area of skin that will then progressively swell over several hours.”¹⁸ More recently, Nielsen *et al.* reported that 15 of 21 of the HAE patients they studied experienced prodromal symptoms of tingling or itching.¹⁹ Based on these articles it appears that prodromal paresthesias are also commonly experienced by HAE patients; however, the specific sensations are variable between individuals and these prodromes do not appear to be an absolute predictor of an attack.

Prodromes of Fatigue and Malaise

A general sense of fatigue or malaise has also been reported as prodromal symptoms that occur before an HAE attack. In the case described by Spaulding, a

27-year-old HAE patient would experience malaise for several hours and up to 1 day before the onset of angioedema.¹⁰ Similarly, Hyman *et al.*, in their report of a case of an HAE patient, identified fatigue as a prodromal symptom.¹³ Subsequent studies confirmed those earlier observations that fatigue or malaise may occur as a prodrome of an HAE attack and that neither is absolutely predictive for an attack. Ohela found that 5 of 27 HAE patients surveyed felt tired for 1–2 days before an attack.²⁶ Similarly, Nielson *et al.* reported that malaise for 1–4 hours before an attack had been described by an unspecified number of the 21 HAE patients they evaluated.¹⁹

Prodromal Changes in Affect or Perceived Energy or Comfort Levels

Changes in patient affect or perceived energy or comfort levels have been described as prodromal signs and symptoms of HAE attacks. Given such reports, it may be conjectured that prodromal changes in affect may have contributed to the previously common term for HAE that was hereditary angioneurotic edema. Of the 12 families observed by Donaldson and Rosen, they found that “members of at least one affected kindred have noted general irritability for a day or two prior to an attack,”¹² whereas, Beck *et al.*, in their case report series of 4 HAE patients described a prodromal phase in 1 of the 4 patients that had a duration of a few hours before the attack and included a sensation of increased energy.¹⁴ Similarly, a “hyperactive period” was identified by Ohela as an initial phase of a prodrome experienced by one of the five HAE patients who were also noted to experience a prodromal sense of being tired for 1–2 days before an attack. In addition, of the 27 HAE patients studied by Ohela, 1 of the 7 who experienced prodromes was noted to become depressed and nervous before an attack.²⁶ At least two of the more recent studies of HAE patients that have included data regarding prodromes have also identified similar changes. Cicardi *et al.* studied 104 HAE patients and reported that 57% described prodromes that included “a feeling of ‘discomfort’ and anxiety, starting 24 hours before the swelling.”⁵ Similarly, Nielson *et al.* found that an unspecified number of the 21 HAE patients surveyed reported experiencing irritability lasting 1–4 hours before the onset of an attack.¹⁹

Prodromes Reflecting Changes in the Gastrointestinal Tract and Fluid Shifts

Given the high frequency of abdominal HAE attacks and the fluid shifts associated with the acute onset of angioedema, there have been relatively few reports of prodromes that we uncovered that reflect changes in the gastrointestinal tract or fluid compartments. However, there have been several such prodromes de-

scribed in the literature. Spaulding reported two cases of HAE patients, one of which inconsistently had prodromal symptoms that included anorexia and nausea that would occur within 24 hours before the onset of an attack.¹⁰ Nausea, as well as abdominal distension, diarrhea, or constipation were reported by Landerman to occur for 3–4 hours before the onset of abdominal pain in an HAE patient.²⁵ Dennehy also reported a case of an HAE patient who had a prodromal sense of bloating and gassiness before an abdominal attack,²⁷ whereas Donaldson and Rosen found that several of the 47 HAE patients they studied, “indicated that a feeling of indigestion or ‘nervous stomach’ may be a warning of the beginning of an abdominal attack.”¹² A sensation of hunger has also been reported by Beck *et al.* as one phase of a prodrome before an abdominal attack in one of four cases described while thirst and polydipsia were prodromes before abdominal attacks experienced by one of the other patients in the series.¹⁴ The results of the recent study by Nielsen *et al.* also identifies thirst as a prodrome of HAE attacks in 10 of 24 patients they surveyed.¹⁹

Significances

Recent published information describes new therapies that have been or are anticipated to be approved shortly.^{28,29} All of the new therapies are anticipated to be indicated for treatment of acute attacks. It is known from the phase 3 studies performed with these new therapies that the duration of time from onset of symptoms to when treatment is given determines the duration of time from treatment to first symptom response and complete symptom resolution. It was the intent of this literature review to determine if prodrome symptoms were sensitive and specific and could be used as an indication to start therapy hoping to completely abort symptoms. Unfortunately, the literature does not adequately address sensitivity or specificity of prodrome symptoms. At this time, it is premature to suggest treatment at the onset of prodrome symptoms, but we hope with additional research this may be an alternative therapeutic option in those who do not wish to take prophylactic therapy, but have frequent and or severe attacks and do not wish to wait for the onset of abdominal pain or swelling before initiating therapy.^{28–31}

CONCLUSION

Our review of the literature clearly indicates that there are a wide variety of prodromal signs and symptoms that may occur before the onset of an acute attack of HAE. Their occurrence and expression appear to be highly variable in nature and their reliability as harbingers of an acute attack of HAE remains to be determined. We have not been able to uncover any study

that evaluates prodromes of HAE for sensitivity or specificity or their predictive value toward the identification of the early, preclinically relevant stages of an HAE attack. Given the significant level of morbidity and risk for mortality associated with acute HAE attacks and in light of the increasing availability of effective therapeutic agents for such attacks, future research efforts focused on the identification of specific and sensitive prodromes of HAE attacks is clearly warranted. Such endeavors may provide the evidence necessary for the development of a validated instrument that is highly predictive of impending HAE attacks for which acute therapeutic interventions could be initiated before the onset of clinically significant angioedema.

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