

Frequency, timing, and type of prodromal symptoms associated with hereditary angioedema attacks

Michael J. Prematta, M.D., John G. Kemp, D.O., Joshua G. Gibbs, D.O., Cathy Mende, C.R.N.P., Crystal Rhoads, M.A., and Timothy J. Craig, D.O.

ABSTRACT

Hereditary angioedema (HAE) types I and II are autosomal dominant conditions characterized by recurrent attacks of edema formation in the subcutaneous tissue of the body or walls of the upper respiratory or gastrointestinal tract. Frequently, prodromal symptoms occur before an HAE attack. If certain prodromal symptoms were determined to be both sensitive and specific in predicting an acute HAE attack, treatment at the time of the prodrome could prevent development of an attack and decrease morbidity and mortality associated with HAE. The goal is to determine the frequency and timing of prodromal symptoms occurring before HAE attacks. After Institutional Review Board approval, a four-page survey was produced, using a focus group of patients with HAE and was assessed by HAE patients and physicians with expertise in HAE for cognitive reliability. Once devised, the questionnaire was sent to 158 HAE patients. The survey focused on questions related to prodromal symptoms that patients developed before their last HAE attack. Forty-six patients returned the survey and 40 (87.0%) reported the presence of prodromal symptoms before their last HAE attack. Forty-four of 46 (95.7%) reported having had prodromal symptoms before HAE attacks in the past. The most commonly reported prodromal symptoms included unusual fatigue, rash, and muscle aches. Prodromes occur frequently before HAE attacks. This high frequency suggests that prodromal symptoms could be a reliable indication to begin treatment to prevent an acute HAE attack, thus decreasing the anxiety associated with having an HAE attack.

(Allergy Asthma Proc 30:506–511, 2009; doi: 10.2500/aap.2009.30.3279)

Key words: C1 esterase inhibitor deficiency, C1 inhibitor deficiency, HAE, HAE attack, hereditary angioedema, hereditary angioneurotic edema, prodrome, prodromal symptoms, symptoms, treatment

Hereditary angioedema (HAE) is an autosomal dominant condition caused by a quantitative or qualitative deficiency of C1-esterase inhibitor (C1-INH). C1-INH is the main regulator of the early steps of the classic complement pathway. Without C1-INH, uncontrolled activation of the classic pathway of the complement system can occur, along with the activation of other inflammatory mediators. In addition to the suppressive effect on the complement pathway, C1-INH also inhibits the kallikrein-kinin system, bradykinin activation, lectin pathway, plasmin, and factors 11a and 12a of the coagulation pathway. Presently, the unregulated activation of bradykinin is thought to

cause the changes we call angioedema.¹ Angioedema can either occur spontaneously or after a traumatic or stressful event, which leads to edema formation. The condition is characterized by acute episodes of sudden edema formation in the skin or in the walls of the upper respiratory tract or gastrointestinal tract. Cases of laryngeal edema can rapidly become life-threatening. Cases of gastrointestinal edema have been misdiagnosed and have led to unnecessary surgeries.² The clinical course, triggers, and frequency of attacks can be difficult to predict. The approach to treatment has two main goals: one is to prevent acute attacks of HAE from developing, and the other is to rapidly terminate acute angioedema attacks if they do occur.

The current treatment options for acute attacks in the United States are limited, but several therapies are likely to be approved in the near future. Two companies are currently producing C1-INH purified from human plasma concentrate. CSL Behring (King of Prussia, PA) is producing Berinert P, which has been available in Europe for many years,³ and Viropharma (Exton, PA) is producing Cinryze.⁴ Both medications have undergone clinical trials and are currently being evaluated for approval by the Food and Drug Administration. In addition to these therapies, several other therapies are being studied including recombinant C1-

From the Penn State Milton S. Hershey Medical Center, Section of Allergy and Immunology, Hershey, Pennsylvania

Poster presentation at the annual meeting of the American College of Allergy, Asthma, and Immunology, November 9, 2008, Seattle, Washington

Financial support for this research endeavor was funded by an unrestricted grant from CSL Behring

T. Craig has received grant/research support from, and is a consultant for CSL Bering, Dyax, Pharming, Jerini, and Viropharma, Jerini and ViroPharma. M.J. Prematta, J.G. Kemp, J.G. Gibbs, C. Mende, and C. Rhoads have nothing to disclose pertaining to this article

Address correspondence and reprint requests to Timothy J. Craig, D.O., Penn State Milton S. Hershey Medical Center, Section of Allergy and Immunology, 500 University Drive, Hersey, PA 17033-0850

E-mail address: tcraig@psu.edu

Copyright © 2009, OceanSide Publications, Inc., U.S.A.

INH (Rhucin, Pharming, The Netherlands),⁵ Kallikrein inhibitor (Ecallantide, Dyax, Cambridge, MA),¹ and a bradykinin-2 receptor antagonist (Icatibant, Shire, Germany).⁶ All of the aforementioned products have been shown to be effective in the treatment of acute HAE attacks, and plasma-derived C1-INH products have also been shown to be effective at preventing acute HAE attacks if given at regular intervals once to twice weekly.^{7,8}

Several authors have described prodromal symptoms that patients with HAE develop minutes to hours before developing an acute angioedema episode. Many of them have described erythematous rashes before the development of edema. These rashes have presented as erythema,⁹ erythematous welts,¹⁰ and erythema marginatum-like rashes.^{11,12} Some of these rashes originated at the site of subsequent angioedema formation, but others did not. In addition, prodromal paresthesias, tingling, or stinging have also been described.¹³ Fatigue and malaise have been described.¹⁴ Other case reports documented gastrointestinal symptoms including nausea, vomiting, or abdominal distention before the onset of an HAE attack.¹⁵ One group surveyed patients with HAE and found that 21 of 21 surveyed said that they did have prodromal symptoms before HAE attacks some of the time and 5 of 21 reported having prodromal symptoms before all HAE attacks.¹⁶ As mentioned previously, plasma-derived C1-INH, recombinant C1-INH, Ecallantide, and Icatibant have been given for the treatment of acute attacks. If there was better understanding of the timing and frequency of prodromal symptoms and their relationship to acute attacks, perhaps a better option for some patients could be the administration of therapy at the onset of prodromal symptoms before acute symptoms develop. Our goal is to gather information regarding the frequency, type, and timing of prodromal HAE symptoms to further evaluate if treating HAE patients based on specific prodromes would be an appropriate indication.

METHODS

After Institutional Review Board approval, a four-page survey was produced using a focus group of five patients with HAE and was assessed by three patients with HAE and three physicians with expertise in HAE for cognitive reliability. Once devised, the questionnaire was sent to 158 HAE patients. The survey asked patients to identify the location of their most recent and most frequent acute HAE attacks. Subjects indicated the location by circling one of the following: abdomen, face, hands/feet, larynx (throat), or other. The survey also questioned the presence of several prodromal symptoms before their last HAE attack and whether they experienced those prodromal symptoms never,

before some, before most, or before all HAE attacks in the past. The patients were also asked to describe their prodromal symptoms with a choice of circling one or more of the following: headache; upset stomach or nausea; abdominal cramps; numbness or tingling in the hands; numbness or tingling in the toes or feet; numbness or tingling over the areas of the upcoming attack; joint pain; muscle aches; rash on the arms or legs; rash on the face; rash on the back, arms, or stomach; unusual fatigue; or other. Subjects were also questioned on the number of hours between the onset of prodromal symptoms and the onset of an attack—considering both their last HAE attack and the most common timing before all HAE attacks. The subjects were given choices of the following: more than 48 hours, 36–48 hours, 12–24 hours, <12 hours, no signs or symptoms before the attack, or do not recall. The last question asked the frequency that patients were able to predict their attacks based on prodromal symptoms in the past with the following choices: unable to predict an upcoming attack, able to predict 25% of the time, able to predict 50% of the time, able to predict 75% of the time, or able to predict 100% of the time. The answers of the anonymously returned questionnaires were then reviewed by our group to determine the frequency, location, and timing of prodromal symptoms.

RESULTS

Forty-six patients returned the survey. Forty of 46 patients (87.0%) reported having had a prodromal symptom before their last HAE attack, and 44 of 46 patients (95.7%) reported having had some prodromal symptoms before HAE attacks in the past. Figure 1 illustrates the prodromal symptoms patients reported before their last HAE attack. The most common prodrome reported was unusual fatigue. In the study, 29 of 46 (63.0%) patients reported having unusual fatigue before their last HAE attack, and 26 of 46 (56.5%) patients reported unusual fatigue before most or all of their previous HAE attacks. Only 5 of 46 (10.9%) patients reported never having unusual fatigue before an HAE attack.

Another common prodromal symptom was a rash. Twenty-two of 46 (47.8%) patients reported a rash on their arms or legs, and 15 of 46 (32.6%) patients reported a rash on their back, sides, or stomach before their last HAE attack. In addition, 15 of 46 (32.6%) patients reported a rash on the arms or legs and 15 of 46 (32.6%) patients reported a rash on their back, sides, and stomach before most or all of their HAE attacks. Muscle aching was also a common prodromal symptom reported in 20 of 46 (43.5%) patients before their last HAE attack, and this occurred in 12 of 46 (26.1%) patients before most or all of their previous HAE at-

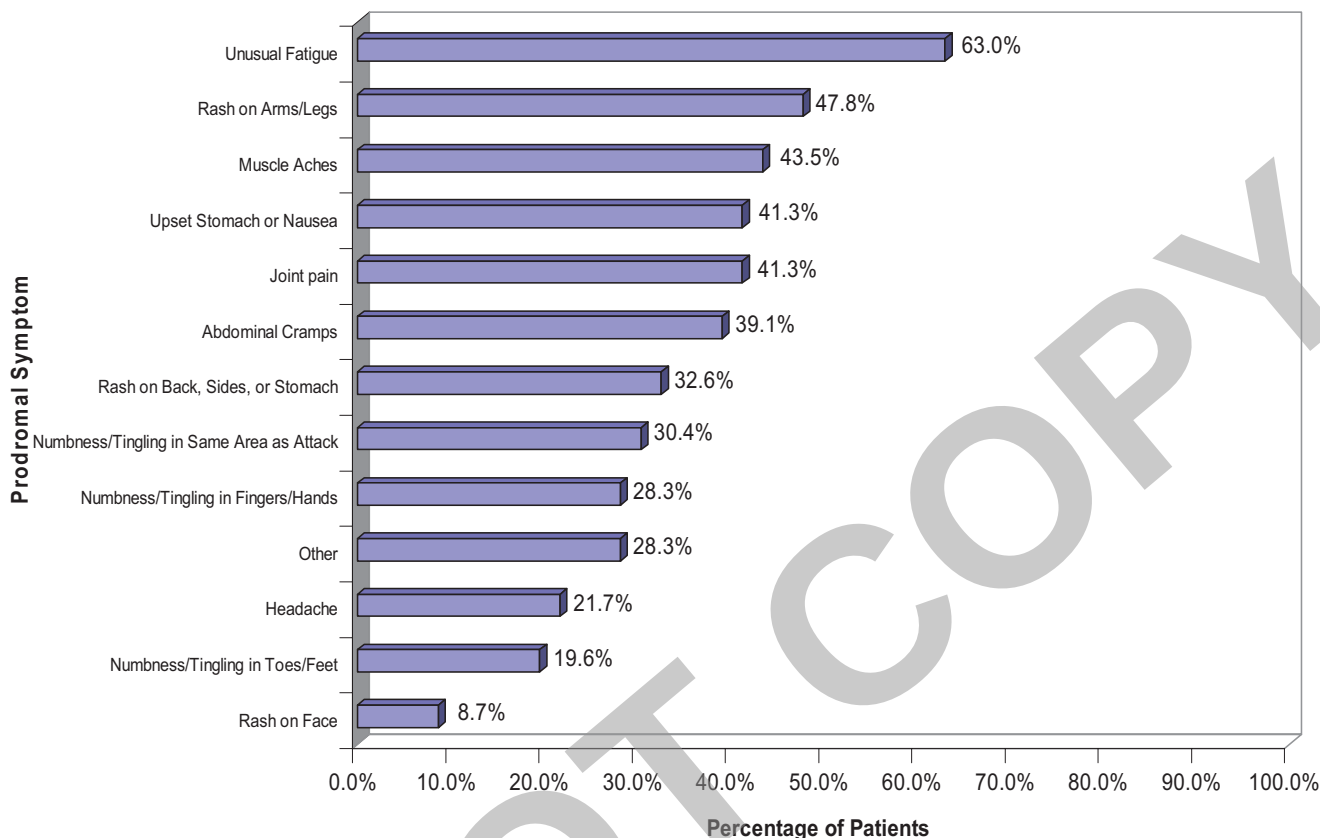


Figure 1. Prodromal symptoms that patients reported before their last hereditary angioedema attack.

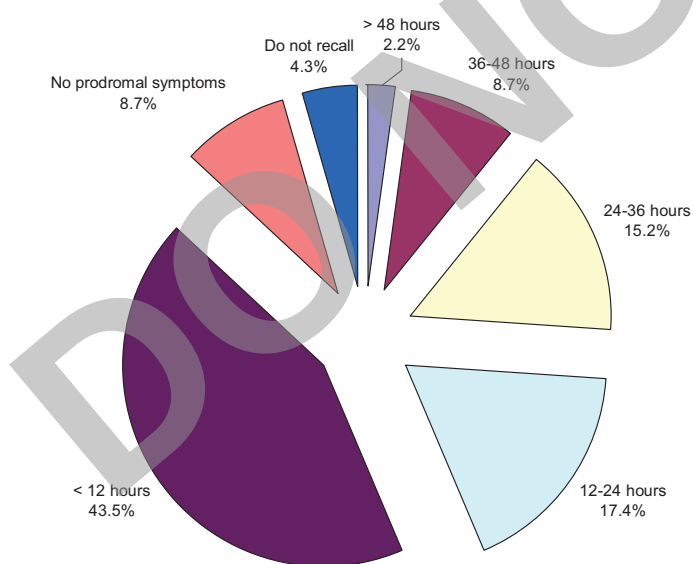


Figure 2. The time between the onset of patient's prodromal symptoms and their last hereditary angioedema attack.

tacks. Other common prodromal symptoms before HAE attacks included upset stomach, nausea, and abdominal cramps.

Figure 2 shows the timing of prodromes before patients' last HAE attacks. The results indicate that 4 of 46 patients (8.7%) did not have a prodrome and 2 of 46

(4.3%) did not remember the timing. Among patients that remembered the prodromal timing before their last HAE attack, 20 of 40 (50.0%) reported a prodrome starting within 12 hours of their HAE attack, and the other 20 of 40 (50.0%) reported that the prodrome started >12 hours before their acute HAE attack.

Figure 3 shows the average timing of prodromes before the development of HAE symptoms. Only 1 of 46 (2.2%) reported not having prodromal symptoms before any HAE attacks, and 1 of 46 (2.2%) did not recall. Among the patients that remembered the timing of past prodromes, 20 of 44 (45.5%) patients reported that the average time of the onset of a prodrome was <24 hours before an HAE attack. Meanwhile, 24 of 44 (54.5%) patients reported that, on average, the onset of prodromal symptoms developed >24 hours before HAE symptoms initiate.

Figure 4 shows the results when patients were asked what percent of the time they were able to predict an HAE attack based on prodromal symptoms. Our results indicate that 3 (6.5%) patients could predict the onset of symptoms 100% of the time; 23 (50.0%) patients answered the ability to predict acute attacks 75% of the time; 4 (8.7%) patients answered 50% of time; and 12 (26.1%) patients answered 25% of the time. Only 4 (8.7%) patients reported not being able to predict the onset of HAE attacks.

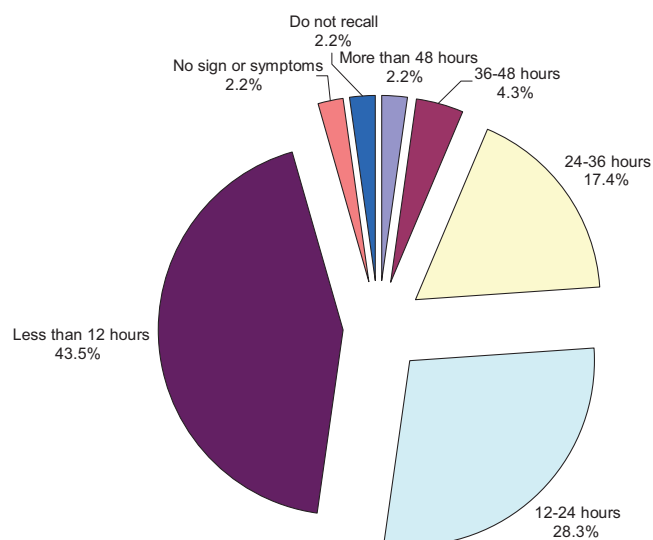


Figure 3. Average time patients reported between the onset of prodromal symptoms and the onset of an acute hereditary angioedema attack.

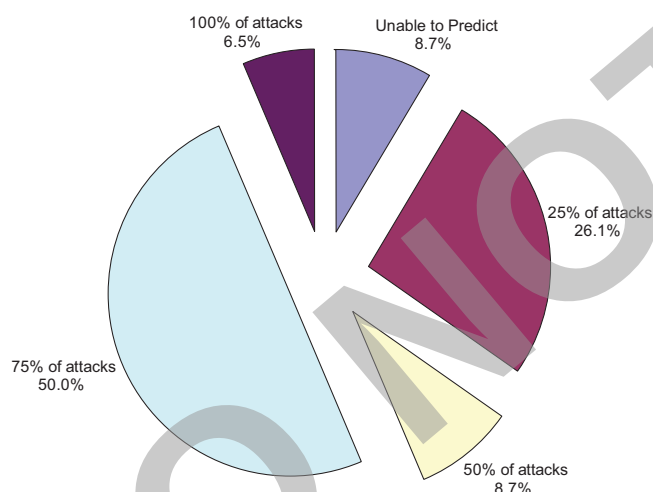


Figure 4. The percentage of time that patients report being able to predict an acute hereditary angioedema attack based on prodromal symptoms.

The locations of patients' last HAE attack is displayed in Fig. 5. The most frequent acute attack locations reported by patients are shown in Fig. 6, and the most common location for an acute HAE attack was the abdomen. It was reported that 26 (56.5%) patients experienced their last attack as abdominal colic, and 29 (63.0%) subjects reported that the most common site for an attack was the abdomen. The hands and feet were the second most common site with 20 (43.5%) patients reporting this as their last attack and 19 (41.3%) patients reporting this as their most frequent attack. The larynx or throat was the least frequent site of acute attacks. Only 1 of 46 (2.2%) patients reported that their last attack was manifested as laryngeal edema, and 4 of 46 (8.7%) patients reported that their

most frequent location of an acute HAE attacks was the larynx or throat.

DISCUSSION

Our data suggest that prodromal symptoms occur commonly before acute HAE attacks with 87.0% of patients having had a prodrome before their last HAE attack, and 95.7% of patients reported having had a prodromal symptom before at least one acute attack in the past. Those with prodromal symptoms may have been more likely to return the survey, so our percentages could be high due to selection bias. On the other hand, because this is retrospective one would think that recall bias would lower the reported frequency. To reduce recall bias, a concern with all retrospective studies, we requested information on the last HAE attack separately from other attacks. The most common prodromes reported are similar to the prodromes found in the literature including extreme fatigue, rash, muscle aches, and nausea or abdominal pain. Although this study is retrospective, it does show strong evidence that prodromal symptoms are a very frequently reported phenomenon among patients with HAE.

As stated earlier, the most intriguing aspect of this topic is to determine if prodromes could be used as a treatment indication. The use of C1-INH in studies has evaluated the use for acute attacks, and the use of scheduled C1-INH infusions, which is given weekly or semiweekly, to prevent acute HAE attacks. Preventative treatment is appealing because patients should experience much fewer and less severe attacks if they do get regular C1-INH infusions. However, the time and cost of those infusions is a potential drawback. If patients are only treated when the attacks occur, this can be life-threatening if they do not receive immediate attention. If prodromal symptoms were determined to be both sensitive and specific, perhaps another treatment option would be to use prodromes associated with HAE as an indication for treatment. This does seem promising, given the fact that over one-half of the patients surveyed reported being able to predict an HAE attack based on prodromal symptoms at least 75% of the time. The other benefit of this treatment option is that HAE attacks would likely be more responsive to treatment if treated early or before the attack ever develops. Bork *et al.* showed that acute attacks treated with C1-INH within 2 hours of the onset of HAE symptoms resolved more quickly than HAE attacks that were treated after 2 hours of onset.¹⁷ If patients were treated based on prodromal symptoms, it possibly would have the benefit of preventing most HAE attacks and patients would not be burdened with the time and financial burden of once weekly or semiweekly infusions. Also, one-half of the patients

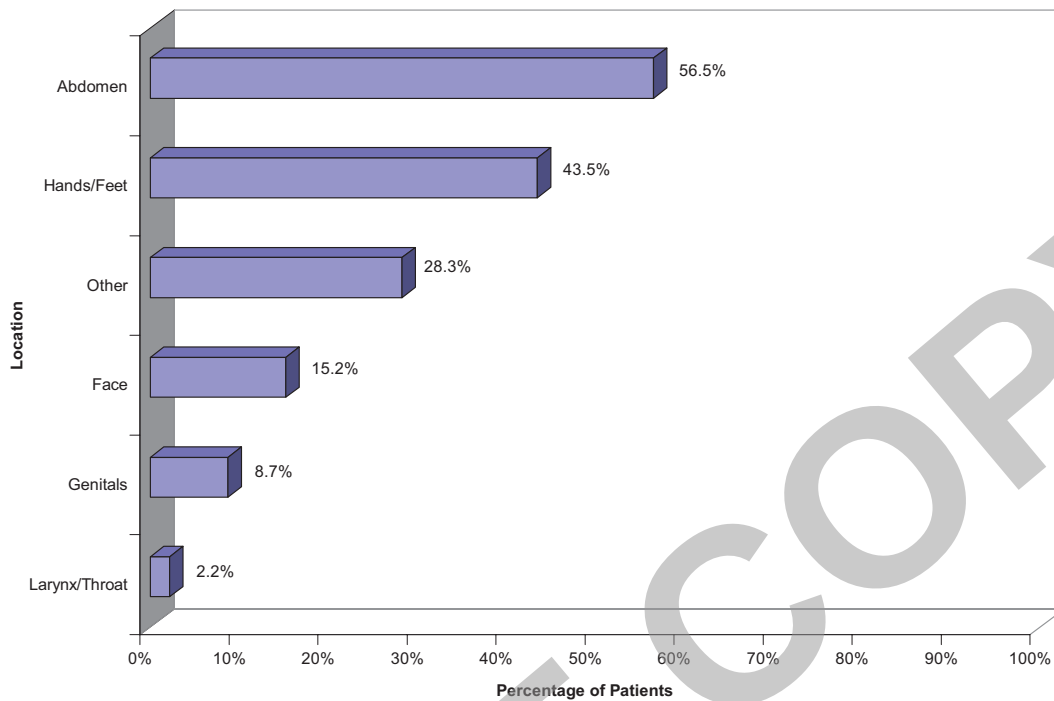


Figure 5. Reported location of patient's last hereditary angioedema attack.

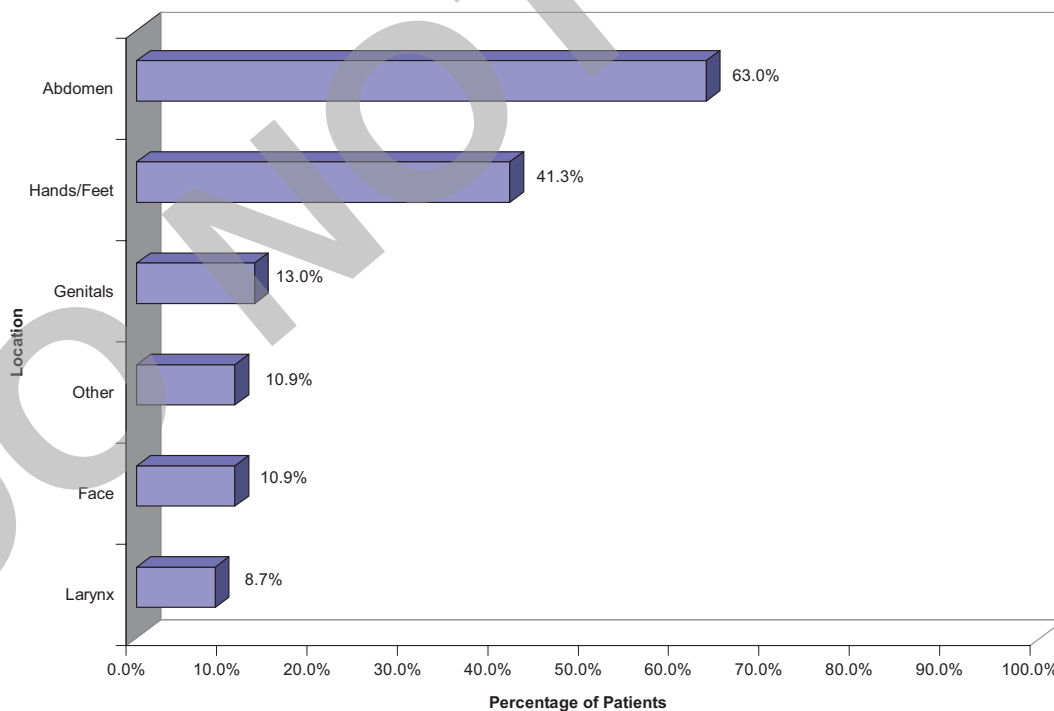


Figure 6. Locations that patients reported as their most frequent hereditary angioedema attack.

reported the onset of prodromal symptoms >12 hours before the onset of an HAE attack. This suggests that patients would often have ample time to get treatment before the onset of an acute attack. For this reason it does appear to be a practical treatment option because many patients claim to be able to predict attacks effectively, attacks treated earlier have been shown to be

more efficacious, and the early timing of prodromal symptoms would allow patients time to get treatment before the development of other symptoms.

Before prodromal symptoms become an indication for treatment, more data would need to be gathered regarding the sensitivity and specificity of prodromal symptoms. From our data, it does appear that prodromal

mal symptoms would be a sensitive measure to predict the onset of an HAE attack; however, specificity can not be inferred from this study. To assess specificity, a prospective study would need to be performed. Patients would need to document every time they had a particular prodromal symptom and every time that they developed an HAE attack. Another study option would be a double-blind placebo-controlled trial where patients were treated with a placebo or C1-INH for prodromal symptoms to determine if there is a reduction in the frequency and severity of attacks with treatment.

CONCLUSION

Prodromal symptoms appear to be very frequent occurrences before the onset of an HAE attack. Results indicate that 87.0% of patients experienced symptoms before their last HAE attack, 95.7% have experienced prodromes before attacks in the past, and 56.5% reported being able to predict an HAE attack based on prodromal symptoms at least 75% of the time. Common prodromal symptoms include unusual fatigue, rash, muscle aches, abdominal pain, and upset stomach or nausea.

The importance of these data are that androgens have multiple associated adverse events and frequently patients are unwilling to use them prophylactically.¹⁷ C1-INH is now available, but the Food and Drug Administration approved for prophylaxis only and not for acute attacks.¹⁸⁻²⁰ Obviously, not all patients meet criteria for C1-INH prophylaxis. The alternative is to wait for symptoms and signs of an acute attack to develop; however, morbidity and mortality are a risk with this scenario. To avoid these consequences, treating at the onset of prodromes may be a cost-effective, reasonable approach for many patients with HAE.

REFERENCES

1. Schneider L, Lumry W, Vegh A, et al. Critical role of kallikrein in hereditary angioedema pathogenesis: A clinical trial of ecalantide, a novel kallikrein inhibitor. *J Allergy Clin Immunol* 120:416–422, 2007.
2. Ohela K, Rasanen JA, and Wager O. Hereditary angio-neurotic oedema. Genealogical and immunological studies. *Ann Clin Res* 5:174–180, 1973.
3. Bork K, and Barnstedt SE. Treatment of 193 episodes of laryngeal edema with C1 inhibitor concentrate in patients with hereditary angioedema. *Arch Intern Med* 161:714–718, 2001.
4. Bernstein JA. Hereditary angioedema: A current state-of-the-art review, VIII: Current status of emerging therapies. *Ann Allergy Asthma Immunol* 100:S41–S46, 2008.
5. van Doorn MB, Burggraaf J, van Dam T, et al. A phase I study of recombinant human C1 inhibitor in asymptomatic patients with hereditary angioedema. *J Allergy Clin Immunol* 116:876–883, 2005.
6. Bork K, Frank J, Grundt B, et al. Treatment of acute edema attacks in hereditary angioedema with a bradykinin receptor-2 antagonist (Icatibant). *J Allergy Clin Immunol* 119:1497–1503, 2007.
7. Bork K, and Witzke G. Long-term prophylaxis with C1-inhibitor (C1 INH) concentrate in patients with recurrent angioedema caused by hereditary and acquired C1-inhibitor deficiency. *J Allergy Clin Immunol* 83:677–682, 1989.
8. Levi M, Choi G, Picavet C, and Hack CE. Self-administration of C1-inhibitor concentrate in patients with hereditary or acquired angioedema caused by C1-inhibitor deficiency. *J Allergy Clin Immunol* 117:904–908, 2006.
9. Frank MM, Gelfand JA, and Atkinson JP. Hereditary angioedema: The clinical syndrome and its management. *Ann Intern Med* 84:580–593, 1976.
10. Cohen JD. Chronic familial giant urticaria. *Ann Intern Med* 54:331–335, 1961.
11. Farkas H, Harmat G, Fay A, et al. Erythema marginatum preceding an acute oedematous attack of hereditary angioneurotic oedema. *Acta Derm Venereol* 81:376–377, 2001.
12. Beck P, Willis D, Davies GT, et al. A family study of hereditary angioneurotic oedema. *Q J Med* 42:317–339, 1973.
13. Crowder JR, and Crowder TR. Five generations of hereditary angioneurotic edema. *Arch Intern Med* 20:840–52, 1917.
14. Ohela K. Hereditary angioneurotic oedema in Finland. Clinical, immunological, and genealogical studies. *Acta Med Scand* 201: 415–427, 1977.
15. Dennehy JJ. Hereditary angioneurotic edema. Report of a large kindred with defect in C'1 esterase inhibitor and review of the literature. *Ann of Intern Med* 73:55–59, 1970.
16. Lunn M, and Craig TJ. Can acute exacerbations be predicted by prodromal symptoms? *Ann Allergy Asthma Immunol*. 100: SA82, 2008
17. Bork K, Meng G, Staubach P, and Hardt J. Treatment with C1 inhibitor concentrate in abdominal pain attacks of patients with hereditary angioedema. *Transfusion* 45:1774–1784, 2005.
18. Craig TJ. Appraisal of danazol prophylaxis for hereditary angioedema. *Allergy Asthma Proc* 29:225–231, 2008.
19. Zuraw BL. Clinical practice. Hereditary angioedema. *N Engl J Med* 359:1027–1036, 2008.
20. Frank MM. New therapies for hereditary angioedema: Disease outlook changes dramatically. *J Allergy Clin Immunol* 121:272–289, 2008. □

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.