

Signs and symptoms preceding acute attacks of hereditary angioedema: Results of three recent surveys

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ABSTRACT

In patients with hereditary angioedema (HAE), premonitory symptoms ("prodromes") may appear hours to days before attack onset. It remains to be determined if prodromes could be useful indicators for early treatment initiation. Most published reports of prodromes have been limited to case reports or small case series. The common objective of several recent survey-based studies was to collect information relevant to prodromal patterns in patients with HAE. Three separate surveys solicited prodromal data from HAE patients. Although differences in survey methodologies permit only descriptive analysis of data, responses to the surveys provide the largest compilation of observational data on this topic to date. Prodromes were reported by 82.5–95.7% of patients surveyed. In one survey, about two-thirds of subjects reported experiencing prodromes before all or most acute HAE attacks, and only 6% of subjects noted the appearance of prodromes in <10% of all attacks. The most common types of prodromal symptoms were related to skin/soft tissue and gastrointestinal tract. Most prodromes were experienced hours to days before the onset of angioedema. A large percentage of surveyed subjects indicated being able to predict an impending HAE attack all or most of the time; <10% reported being rarely or never able to predict an attack. Although insufficient to establish the clinical role of prodromal symptoms, results of these surveys provide additional data on the scope of prodromes and could stimulate further research into the potential efficacy and cost-effectiveness of HAE attack prediction and prodrome-triggered interventions.

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Individuals with hereditary angioedema (HAE) experience spontaneous, recurrent, and sporadic painful attacks of angioedema involving the extremities, genitals, intestinal wall, face, or upper airway. Acute attacks often build in intensity over 12–24 hours and may persist throughout the following 2–3 days.^{1,2} Aside from significant disruptions in lifestyle and work productivity inflicted by HAE attacks, severe episodes can be very painful and deforming,³ and tongue/laryngeal swellings are potentially life-threatening.^{4,5}

HAE attacks are often preceded by signs and symptoms ("prodromes") such as unusual fatigue, reticulate rash (erythema marginatum), abdominal pain, stomach upset, or nausea.⁶ There is increasing interest in gaining a better understanding of whether these prodromes have any value as indicators for instituting

early treatment to prevent acute symptom progression.^{2,6,7} This concept has gained momentum with the availability of on-demand treatments such as C1 inhibitor (C1-INH) concentrate (Berinert; CSL Behring, King of Prussia, PA) and icatibant (Firazyr; Shire Orphan Therapies, Inc., Lexington, MA), which can be administered at home by the patient.^{8–11} Until recently, clinical study data about prodromes had been limited to a few case reports or small case series.^{12–19} These data suggest that prodromes reported by patients are relatively frequent but have a wide variability of subjective and objective manifestations.

This article presents the results of three recent surveys that sought to capture histories and patients' perceptions of prodromes associated with HAE attacks. These surveys were completed independently of each other. As such, there are variations in methodology and terminology that did not allow a formal, pooled analysis of data. The intent of presenting the findings together is to raise awareness of the prodrome phenomenon, highlight any apparent consistencies in prodrome patterns, and, hopefully, stimulate and facilitate ongoing research in this area.

METHODS

Methods Survey 1

This retrospective survey was conducted among a cohort of HAE patients affiliated with the Allergy, Immunology and Angioedema Center of Sheba Med-

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ical Center, Tel-Hashomer, Israel. Patients were randomly surveyed in person or through a telephone interview. Written informed consent was provided from all participants, either through the mail or in person. A questionnaire covering organ systems ("clusters") and complaints was selected based on published literature and the Center's clinical experience. For each relevant symptom, the patient was asked to indicate the body location and duration of the prodrome. In addition to each "cluster" of signs and symptoms, the questionnaire sought information about the overall prodromal history experienced by each patient. Patients were also asked to indicate what proportion of their HAE attacks were preceded by a prodrome (all, most, less than one-half, <25%, or <10%) and if they were able to predict an acute attack based on prodromal symptoms (absolutely, most of the time, occasionally, or no). Details of the survey are provided in Supplemental Appendix A. Data were analyzed descriptively.

Methods Survey 2

Survey 2 was a prospective, voluntary companion survey of an open-label study of pasteurized C1-INH concentrate at multiple sites in the United States.^{20,21} In this study, patients with HAE attacks at any body site could be treated with open-label C1-INH at 20 U/kg. At the time of treatment, subjects were asked to respond voluntarily to a questionnaire about the presence and nature of prodromes before the current HAE attack (see Supplemental Appendix B for questionnaire details). Considering that subjects were relying on their recent memory (within 36–48 hours), survey 2 was the most prospectively designed assessment of HAE prodromes of which the authors are aware. Participants who indicated having had a prodromal event were questioned about the type of symptom or sign and its duration before the HAE attack.

Methods Survey 3

Survey 3, conducted by the Pennsylvania State University Asthma, Allergy, and Immunology Department, was a retrospective questionnaire sent by mail to 158 HAE patients.⁶ The survey requested information about prodromal events before patients' most recent HAE attacks. The survey was developed by a group at Pennsylvania State University who specialize in survey design, along with a focus group consisting of patients with HAE and caregivers that provide care for HAE. The instrument was tested in a small cohort of patients and their answers were discussed with them to ensure the survey was obtaining the intended information. The survey was at an appropriate reading level for a

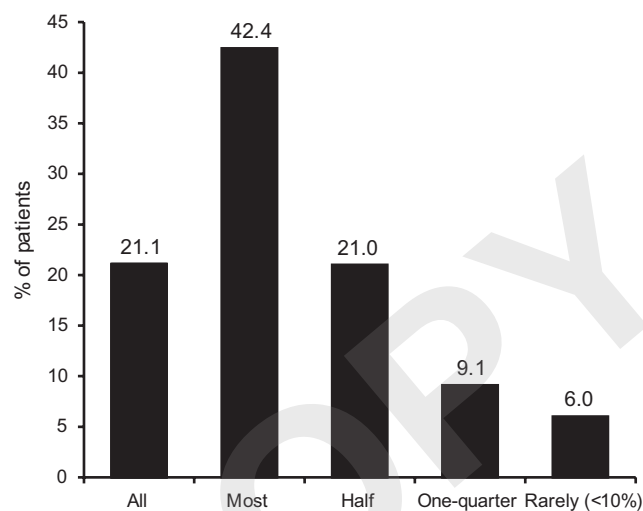


Figure 1. Reported frequency of hereditary angioedema (HAE) attacks preceded by prodromes among 33 of 40 subjects who reported ever having prodromes (survey 1).

12-year-old (see Supplemental Appendix C for questionnaire details).

Survey responders were asked to indicate the nature of the prodrome(s), the amount of time from the onset of a prodrome to the acute attack, and what percentage of attacks were associated with a prodrome. To reduce recall bias, we collected recent and more historic data separately.

All three studies were approved by institutional review boards.

RESULTS

Survey 1

A total of 40 HAE patients (20 men and 20 women) participated in the survey. Mean age of the study population was 28.8 years (SD, 18.5 years; range, 1.5–64.0 years), and the mean duration of HAE was 20.6 years (SD, 17.0 years). Thirty-three (82.5%) subjects indicated having experienced a prodrome at least once in the past, and 17.5% reported never having had prodromes. Among subjects with a history of prodromes, 63.5% indicated experiencing prodromes before all or most of their attacks (Fig. 1). A large majority (84.5%) reported that prodromes were associated with at least one-half of all attacks. In response to the question, "Can you predict an oncoming attack?" 21 (63.6%) subjects responded "yes" and another 6 (18.2%) indicated "most of the time."²²

The body systems most commonly reported to be ever affected by prodromal signs and symptoms were skin and soft tissue (78.8% of subjects reporting), gastrointestinal (GI; 60.6%), emotional/psychological (30.3%), and musculoskeletal (27.3%; Fig. 2). Fewer patients reported ever having had prodromes affecting the respiratory, neurological, urinary or

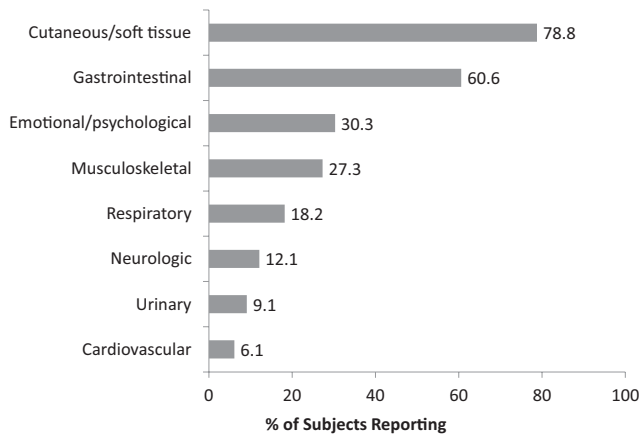


Figure 2. Reported prodrome frequency categorized by body system (survey 1).

cardiovascular systems. Pruritus and rash were the most commonly reported prodromes (42.4% of subjects reporting both), followed by GI pain/pressure (39.4%), itch and nausea (both 33.3%), appetite changes and fatigue (both 30.3%), and flu-like symptoms (27.3%; Table 1).

Results of Surveys 2 and 3

Two authors (M.P. and T.J.C.) were involved in two other recent surveys designed to solicit information about prodrome frequency and patterns. Common categorical data from these two surveys have been combined into a single database for more robust analysis and are presented here for a rudimentary comparison with the findings from survey 1.

The prospective survey 2 included data reflecting 253 acute HAE attacks in 21 patients, and the retrospective survey 3 represented 52 acute HAE attacks in 52 patients.²³ More than two-thirds (70.5%) of attacks listed in the surveys developed after a prodrome. The most commonly reported prodromes were fatigue (45%), GI complaints (41%), muscle aches/flu-like symptoms (26%), and rash (21%). Figure 3 compares the incidence of prodromes cited in survey 1 with the incidence of the same types of prodromes in surveys 2 and 3. In 69% of cases in studies 2 and 3, the time lapse between prodromal symptom appearance and the onset of an acute HAE attack was <24 hours, and in 39% of attacks this interval was <12 hours (Fig. 4). The interval between prodrome and acute event was rarely >36 hours (1% of attacks), and it never surpassed 48 hours.

DISCUSSION

Prodromes are frequently reported by HAE patients, as well as by patients with other chronic disorders characterized by recurrent attacks (*i.e.*, epilepsy, Familial Mediterranean Fever, migraine,

Table 1 Prodromal events most commonly reported (frequency >10%) among 33 surveyed HAE patients who reported ever experiencing prodromal symptoms* (survey 1)

Prodrome	n (n = 33)	Percent of Patients
Pruritus	14	42.4
Rash	14	42.4
GI pain/pressure	13	39.4
Itch	11	33.3
Nausea	11	33.3
Appetite changes	10	30.3
Fatigue	10	30.3
Flu-like symptoms	9	27.3
Gas	8	24.2
Nervous	8	24.3
Skin pain	7	21.0
Bad taste	6	18.2
Dry mouth	6	18.2
Anger	6	18.2
Skin warmth	5	15.2
GI urgency	5	15.2
Depression	5	15.2
Paresthesia	4	12.1
Heartburn	4	12.1
Diarrhea	4	12.1
Dizzy	4	12.1

*Other events reported by <10% of patients: flushing, sneezing, runny nose, "ball in throat," (respiratory) itch, shortness of breath, cough, dysphonia, urinary urgency/difficulty/pain/burning, incontinence, limited movement, anxiety, despair, palpitation, chest pain, lightheadedness, faint feeling, and balance problems.

HAE = hereditary angioedema; GI = gastrointestinal.

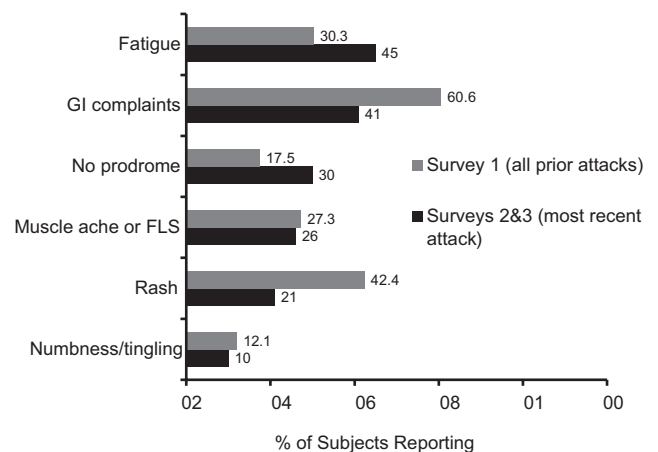


Figure 3. Comparative frequencies of common prodromal symptoms reported in survey 1 (indicative of having EVER experienced before an acute attack) and surveys 2 and 3 (most recent attack only).

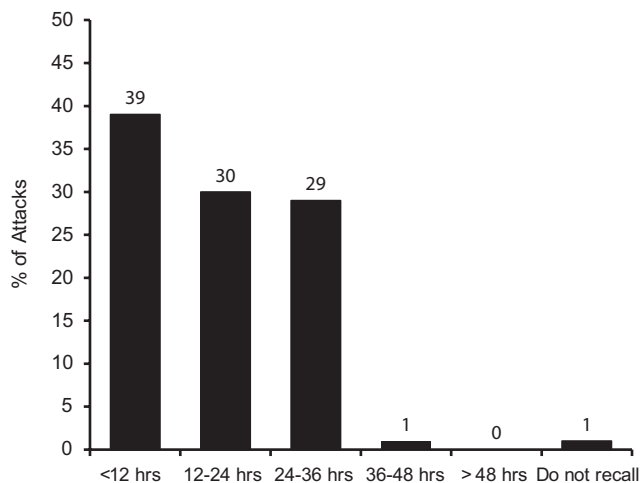


Figure 4. Amount of time reported between awareness of prodromal symptom(s) and the onset of an acute hereditary angioedema (HAE) attack ($n = 402$ prodromes), percentage of patients reporting within each time period (surveys 2 and 3).

etc.).²⁴ Until recently, published information about HAE prodromes has only been in the form of anecdotal case reports or small case series.^{12–19} Recent interest in the clinical value of prodromes has prompted more purposeful clinical research in several larger cohorts, although the size of such groups is still limited by the rarity of HAE. A scientifically rigorous pooling and analysis of prodromal data from these different surveys of patients experiencing prodromes would be desirable, but doing so is complicated by protocol disparities such as different survey techniques, inconsistent nomenclature, and poorly defined prodrome categories. Two of the three surveys were retrospective in nature, relying on patient memory and potentially affected by recall bias. Although survey 2 was prospective, it only captured prodromal information associated with attacks severe enough to seek treatment. Survey 2 also collected data at the time of an attack; although this was intended to minimize recall bias, it is possible that some patient responses also could have been negatively affected by the acute distress of the attack. These limitations restricted our analysis to a descriptive presentation of findings, which, although not conclusive, contribute to the growing body of evidence attesting to the importance of HAE prodromes.

The limitations of the survey characteristics did not allow us to determine prodrome specificity; however, these data focus on outcomes having reasonable clarity, especially for sensitivity. From these data it seems clear that prodromes are experienced to some degree by most patients with HAE and precede the majority of attacks. In survey 1, in which the mean duration of HAE was 20 years, 82.5% of respondents reported having ever experienced prodromes in association with acute attacks.²² In the

retrospective survey 3, the percentage was even higher (95.7%).⁶ The disparity in reported prodromal frequency could certainly reflect the differences in the survey methods. Survey 1 was conducted through personal encounters or by telephone, whereas survey 3 was a mail-based questionnaire.^{6,22} It is possible that the people most likely to return the mail survey were those who actually experienced prodromes, making the percentage of positive responses higher. In survey 2, in which patients submitted recent data on an attack-by-attack basis, 15 of 21 (71.4%) patients reported a prodrome associated with at least one attack. In survey 1, about two-thirds of respondents indicated that all or most of their HAE attacks were preceded by a prodrome.

The overall pattern of prodromal symptoms identified in the surveys described here is consistent with previously reported data. A review of relevant literature published between 1950 and 2007 found the most frequently reported prodromes to be rashes (i.e., erythema marginatum), followed by paresthesias, GI complaints, fatigue/malaise, and changes in mood/emotions.² Data from the three surveys reveal a similar pattern, with cutaneous symptoms/rash and GI complaints being most commonly noted. The incidence of GI-related prodromal events was notably higher in survey 1 (60.6%) than in surveys 2 and 3 (41%), a finding that might be related to differences in questionnaire design. The questionnaire used in survey 1 included nine individual items under the “gastrointestinal cluster”; in contrast, survey 2 offered only three GI symptom options, and survey 3 listed only two such symptoms. Furthermore, survey 1 retrospectively encompassed the subjects’ entire history of HAE attacks, not just the most recent event, raising the likelihood of subjects reporting GI-related prodromes. Conversely, the greater percentage of patients in surveys 2 and 3 reporting “no prodrome” could be caused by their considering only their most recent attacks, and not their entire recollection, as in survey 1.²² Additionally, surveys relying on patient memory may suffer from inaccuracies and should be interpreted with caution.

Given the fact that prodromal symptoms are mostly subjective (as opposed to clinical findings), the most clinically relevant question posed in the surveys is, “Can you predict an oncoming attack?” In survey 1, 83% of patients indicated feeling able to predict an oncoming attack all or most of the time. In survey 3, 57% of respondents indicated feeling able to predict an acute attack at least 75% of the time.⁶ (Survey 2 did not address this question.) The percentages of patients in survey 1 and survey 3 who felt rarely or completely unable to predict an oncoming attack were only 6 and 8.7%, respectively.⁶ Future studies should investigate the relationship be-

tween subjective signs (*i.e.*, pruritus) and objective findings (*i.e.*, erythema marginatum rash) and to what extent these prodromes are followed by an acute attack. International HAE clinical recommendations advocate self-treatment as the optimal treatment modality for acute HAE, based on the notion that it permits intervention at the earliest time point possible to maximize treatment response.^{25–27} Therefore, identifying early signs and symptoms of an upcoming attack could allow for better response to treatment and possibly lessen morbidity and mortality associated with HAE attacks. Such an approach, albeit promising, could be applied only when prodromal signs and symptoms are better characterized, their specificity determined, and their relationship to the pathological process of tissue edema clarified. The concept of being able to halt an impending attack on the appearance of prodromal symptoms could theoretically combine the best features of on-demand management of HAE.

Indeed, evidence suggests that early intervention can lessen the duration and severity of HAE attacks.^{8,9,28,29} However, it should be cautioned that prodrome-triggered intervention may occasionally result in unnecessary drug administration and the cost-effectiveness of such a strategy has not been evaluated. On the other hand, the early recognition of prodromes can allow patients to better prepare for an oncoming attack and commence appropriate action. Additionally, applying self-management protocols, based on training to assess a progressing attack and early intervention, will raise patients' confidence and reduce apprehension and anxiety. Clearly, more purposeful studies are needed to solidify objective and subjective definitions of prodrome signs and symptoms, obtain better insights on the pathophysiology of prodromes, and determine temporal relationships between prodromes and attacks and possible correlations with disease severity, location, and treatment outcomes. The ultimate goals of such research would be to define the specificity, sensitivity, and predictive values of prodromes, as well as to investigate the effects of all these factors on patient quality of life.

The findings presented here, although not capable of fully characterizing the potential of HAE prodromes, add to and corroborate the growing body of data on this subject. Our data suggest that prodromes in HAE are more common than has often been assumed and that a majority of HAE patients report being able to predict most of their attacks, emphasizing the importance of well-designed, focused research in this area. We hope that our findings will spur continued interest in HAE prodromes, as well as the clinical efficacy, cost-effectiveness, and

quality-of-life impact of a prodrome-based treatment approach.

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