Prodromal Symptoms of Hereditary Angioedema (HAE) attacks: a patient survey in UK & Spain

Guilarte Mar1 and Patrick Yong2

1Vall d’Hebron Institut de Recerca
2Frimley Health NHS Foundation Trust

May 4, 2023

Abstract

Background: The occurrence of prodromes has been associated with swelling in hereditary angioedema (HAE). The aim of the study was to analyse the frequency of prodromal signs, the level of awareness among HAE patients and to understand the actions taken by patients when they experienced them. Methods: An online survey to assess patient experiences of prodromal symptoms was conducted among 208 HAE patients from the UK and Spain. Results: 60% of HAE patients who experience prodromes can always or usually predict an impending swelling. Almost 40% of participants noticed prodromes within the 2 hours preceding an HAE attack. Tiredness/fatigue (64%), pressure or tightness in the skin (53%) and abdominal pressure (52%) were the most reported early symptoms. C1-esterase inhibitor (C1-INH) and icatibant were prescribed to 75% and 65% of participants, respectively. 56% of participants in the UK reported self-medicating at the time of prodrome, whereas 65% of patients in Spain preferred to wait or relax when early symptoms began. 30% of patients said they usually took their medication within 1 hour of experiencing the prodrome. The percentage of patients who needed only one injection to treat the attack increased when patients took their medication early in the prodrome (from 55 to 66%). Conclusions: The majority of patients who have early symptoms were usually or always able to predict that a swelling would occur. Early treatment of HAE attacks is associated with less medication usage, but there is still no common understanding of what ‘early treatment’ means.

Patrick FK Yong (ORCID ID: 0000-0003-1736-2756)
Guilarte Mar (ORCID ID: 0000-0001-7242-9584)

Manuscript title

Prodromal Symptoms of Hereditary Angioedema (HAE) attacks: a patient survey in UK & Spain

Running title:

Prodromal symptoms of HAE attacks - a patient survey

Authors

Patrick FK Yong1 and Guilarte Mar2*

Affiliations

1 Immunology Department, Frimley Health NHS Trust Foundation, Frimley GU16 7UJ, UK
2 Allergy Department, National Reference Hereditary Angioedema Center (CSUR), Hospital Vall d’Hebron. Vall d’Hebron Research Institute (VHIR). Barcelona, Spain

Correspondence

*Mar Guilarte
Abstract

Background: The occurrence of prodromes has been associated with swelling in hereditary angioedema (HAE). The aim of the study was to analyse the frequency of prodromal signs, the level of awareness among HAE patients and to understand the actions taken by patients when they experienced them.

Methods: An online survey to assess patient experiences of prodromal symptoms was conducted among 208 HAE patients from the UK and Spain.

Results: 60% of HAE patients who experience prodromes can always or usually predict an impending swelling. Almost 40% of participants noticed prodromes within the 2 hours preceding an HAE attack. Tiredness/fatigue (64%), pressure or tightness in the skin (53%) and abdominal pressure (52%) were the most reported early symptoms. C1-esterase inhibitor (C1-INH) and icatibant were prescribed to 75% and 65% of participants, respectively. 56% of participants in the UK reported self-medicating at the time of prodrome, whereas 65% of patients in Spain preferred to wait or relax when early symptoms began. 30% of patients said they usually took their medication within 1 hour of experiencing the prodrome. The percentage of patients who needed only one injection to treat the attack increased when patients took their medication early in the prodrome (from 55 to 66%).
Conclusions: The majority of patients who have early symptoms were usually or always able to predict that a swelling would occur. Early treatment of HAE attacks is associated with less medication usage, but there is still no common understanding of what ‘early treatment’ means.

Keywords
Early signs and symptoms, Hereditary angioedema, HAE, Prodromes, Treating early

Introduction
Hereditary angioedema (HAE) is a rare, potentially life-threatening disease with an estimated worldwide prevalence of 1:50 000. HAE is characterized by recurrent, transient episodes of subcutaneous or submucosal nonpruritic swelling that resolve spontaneously in 2-5 days. The areas typically affected include the extremities, gastrointestinal tract, face, genitals, as well as larynx. The frequency, location and severity of attacks vary unpredictably and the clinical phenotype differs from patient to patient.

Emotional distress, physical trauma, infections or changes in oestrogen levels have been identified as the most frequent precipitating factors although 50% of attacks do not have recognized triggers. The number of attacks differs from patient to patient, but when not treated, attacks can appear every 7 to 14 days on average with frequency ranging from virtually never to every 3 days. Usually, the swelling worsens progressively over the first 24 hours, then slowly subsides over the subsequent 48 to 72 hours. Aside from significant disruptions to everyday life, severe episodes can be extremely painful and disabling; and laryngeal swellings can cause asphyxiation or permanent brain damage.

Recent data suggests that more than 80% of HAE patients may experience prodromes, also referred to as early symptoms or signs, that precede the swelling attack. The most common include tiredness, irritability, erythema marginatum (EM), tight or tingling sensation in the skin, abdominal discomfort, and nausea. Previous studies confirmed that prodromes are more frequent than initially realized and a significant correlation was shown between the perception of prodrome and the ability to predict an oncoming swelling. Of all the above-mentioned early symptoms, EM is the only objective phenomenon. Pathophysiologic changes, such as elevation of D-dimer levels begin during EM development and thus, EM may actually be regarded as the initial phase of an HAE attack, not a separate entity.

These findings are of importance considering the widespread availability of treatments for on-demand use, such as C1 esterase inhibitor (C1-INH) concentrate and icatibant, which can be administered at home by the patient. Early treatment of HAE attacks with icatibant, particularly within the first hour of attack onset, significantly reduced attack duration and time to attack resolution. Accordingly, prodromes may alert patients of forthcoming attacks and allow them to deploy therapeutic strategies to avoid or shorten them. Unfortunately, limited research has been done on prodromes in HAE and they remain mostly subjective with their contribution to treatment disputed.

This article presents the results of a patient-focused survey, which sought to characterize levels of awareness of prodromal symptoms amongst HAE patients to understand what kind of symptoms HAE patients may experience prior to swellings and how patients managed early signs and symptoms.

Materials & Methods
Following discussions with expert physicians, nurse specialists and patients, an anonymous survey was performed to assess the real-world patient experience of HAE and the early symptoms/signs of attacks. The survey questionnaire was approved by HAE UK and the Asociación Española De Angioedema Familiar (AEDAF), the local HAE patient organizations. Invitations to participate containing a secure link to an online survey were sent via e-mail to their membership databases. Informed consent was obtained for all participants before accessing the survey.

In order to be eligible, patients had to be at least 16 years old, diagnosed with HAE, taking medication for HAE and to have previously experienced a prodromal sign or symptom of an attack.
Data collection took place in February 2022 in the UK and May 2022 in Spain and was analysed descriptively.

Results

Population characteristics

A total of 208 HAE patients participated in the survey, 128 (61%) were from the UK and 80 (39%) from Spain. For both UK and Spain, 65% of participants were females and 35% were males. The mean age of participants was 46 years (range 16-79). Participants had been diagnosed with HAE for a mean of 25±13 SD years. The majority of patients (65%) had a university, post-graduate or professional qualification. Most (over 80%) lived with their family or partner, whereas 14% lived on their own.

61% of respondents were professionally active with 45% employed full-time and 16% - part-time. More than half of the participants (61%) engaged frequently in physical activities such as exercise, sports, manual work, or hobbies that demand physical effort, however, males (78%) seemed to be much more likely to engage in physical activities than females (52%) (Supplementary Table 1).

Interestingly, 48% of patients said HAE impacts their ability to live their lives a lot (14% very much and 34% quite a lot) and female participants (54%) are more impacted than males (39%). Just 5% said that disease does not impact their ability to live their life the way they want at all. Nevertheless, the majority (70%) declared feeling that they manage their disease very well (30%) or quite well (40%). However, more UK patients felt that they are managing their HAE better than Spanish patients (80% vs 52%; Supplementary Table 1).

Access to treatment and management of HAE

68% of HAE patients had seen an HAE- HCP specialist within the last 5 months prior to the survey (59% in the UK, 82% in Spain). The vast majority of participants (91%) had their last HAE attack within the previous 12 months and almost a third of participants categorized their last HAE attack as severe (Supplementary Table 1).

The most commonly prescribed treatments were C1-INH (Berinert®, CSL Behring, Cinryze®, Takeda and Ruconest®, Pharming) and icatibant (Firazyr®, Takeda), with 75% and 65% of participants receiving them respectively. Over half of HAE patients were prescribed more than one type of treatment. 18% of participants were using danazol (mostly males). Details of all the treatments prescribed are available in Supplementary Figure 1.

The majority of HAE patients (78%) administered the medication themselves (86% UK, 65% Spain). 13% of patients have their medication administered by an HCP; this happened more often in Spain (25%) than in the UK (6%). Moreover, there were striking differences in the means of obtaining prescriptions between the two countries. Among the UK participants, 73% have their medication delivered to them compared to 46% of patients in Spain, whilst only 17% of patients in the UK collected it from their medical centre compared to the majority of patients (65%) in Spain.

Overall, 79% of surveyed patients felt their needs were well understood by HCPs and they had high levels of satisfaction with the medical treatment and advice they had been given (87% and 92%, respectively).

Awareness and experience of prodromal signs and symptoms

Of the patients surveyed, 60% were usually aware of early signs/symptoms before swelling began, including 19% who said they were always aware. In terms of the time before the swelling started, 38% of participants noticed prodromes within 2 hours, a further 27% between 2 and 6 hours, and 29% more than 6 hours before the swelling started. Interestingly, in the UK females tended to become aware of prodromes earlier than males (>2 hours before swelling; 61% females vs. 47% males), whereas, in Spain, the opposite was seen (46% females vs. 70% males).

Participants experienced a broad range of early signs/symptoms. Feeling tired/fatigued was the most frequently reported prodromal symptom (64% overall; 71% female and 52% male), followed by pressure or
tightness in the skin (53%), pressure in the abdomen (52%) and widespread pain in the abdomen (48%) (Figure 1). Over a third of participants experienced a skin rash including EM (Figure 1).

The survey also examined the location of HAE swelling attacks themselves. Patients reported that swellings mostly occurred in the abdomen (89%), followed by hands (71%), feet (63%) and then face (40%). A higher proportion of male participants described swelling in their genital area (37%) compared to females (16%).

The reaction of patients to prodromal signs and symptoms

Among surveyed patients, 56% (N=116) felt that early signs/symptoms provided them with a warning that swelling was coming for most of the attacks they experienced. Interestingly, actions taken by patients when prodromes started differ between countries. While over half of the participants in the UK declared taking some form of medication (ranging from HAE-specific treatment like icatibant (32%) to painkillers (4%)), most of the patients in Spain (65%) often took a ‘watch and wait’ approach to early signs, or would try to relax/go to bed or take a bath. Of note, 13% of participants from Spain mentioned that they become anxious or scared in reaction to the early signs (Figure 2).

The overall majority of patients (59%, N=122) declared taking medication when they experienced an early sign/symptom. Of those, 6% stated always taking their medication when experiencing prodromes, 9% doing this for most attacks, 19% for some attacks and 25% for a few of the attacks they had experienced (Figure 3).

Looking at the time participants have taken their medication, 36 patients said that they had typically taken it within 1 hour of first experiencing the early sign/symptom (with half of these patients doing so immediately) and a further 40 patients between 1 and 2 hours after the prodromal symptoms started (Figure 4). It must be noted that these respondents were predominantly from the UK (N=94 vs. N=28). Overall, male participants tended to take their medication earlier than female participants (N=11 vs. N=7) with some taking them immediately after an early sign/symptom started, whilst female participants waited longer, typically taking their medication between 2 and 6 hours after the start of prodromes compared to male participants (N=20 vs. N=6; Fig.4). Notably, although Spanish patients were more reluctant to treat when a prodrome occurred than UK patients, those who decided to treat took the medication more quickly than UK participants (53% vs 35% took the medication between immediately and 2 hours; or 21% vs 13% immediately).

The majority of patients (65% of respondents) said that they had not always been able to take their medicine before a swelling began. For this large sub-group (N=127), we then asked whether they thought they could have avoided or prevented the swelling if they had taken their medicine when they experienced prodromes. It is interesting to note that 35% agreed that they definitely could have avoided swelling, and a further 47%, felt that they could possibly have avoided swelling, by taking the medication at this early point.

The advice of HCP on when to treat the attacks and the number of injections to use

When suffering an HAE attack, 55% (N=111) of participants said that they typically need one injection to treat it, 29% said they needed two injections of their medication, and a further 5% three injections. When taking medication at the onset of early signs and before the swelling has started, 65% (N=76) of participants said they typically need one injection to treat an HAE attack, 21% said they needed two injections, and 6% three injections (Figure 5). This suggests that treating early may reduce medication use to some extent. A higher percentage of female participants (54%) waited for the swelling to start before taking their medication than male participants (44%).

Regarding how patients understand the advice of the HCP, a large majority of HAE patients (70%) said their HCP has advised them to ‘treat early’. Of those, 84% said their HCP explained what they meant by ‘treating early’. However, there remains mixed understanding among participants about what ‘treating early’ meant: 60% thought it meant taking their medication as soon as they experienced an early sign; whilst 26% believed it meant taking their medication if the early signs/symptoms persisted or developed and a further 13% believed it meant taking the medication as soon as the swelling started (Figure 6).
Discussion

The significant progress that has been made in the past decade in elucidating the pathophysiological mechanisms of HAE has led to discoveries of novel therapies providing patients with better on-demand and prophylactic treatment options. As a result, patient care and their quality of life has significantly improved.22 The majority of participants enrolled in the current study were working full- or part-time and they frequently engaged in physical activities. At the same time, there was a very high level of satisfaction among the HAE patients (>90%) regarding the medical care they receive from physicians. Additionally, the majority of participants (70%) felt they manage their disease well. These findings are encouraging and show the significant progress made. However, HAE patients are still profoundly burdened with disease, experiencing frequent and unpredictable attacks and thus, their ability to live their life the way they want remains heavily impacted. Despite the progress made in HAE management, only 5% of participants said the disease has no impact on their everyday life. Thus, improvement in the care of individuals suffering from HAE is still needed.

The perception of prodromal signs and symptoms is unique to each individual patient. However, there is a pattern of early signs and symptoms experienced by majority of patients. These might include malaise, fatigue, changes in mood or emotions, such as sadness and irritability, as well as a tingling sensation and skin rash (i.e. erythema marginatum), abdominal pain or nausea.11,16,23,24 Data from our study revealed a similar pattern, with fatigue, followed by pressure or tightness in the skin, pressure and widespread pain in the abdomen being most commonly noted. Given the fact that there is a wide spectrum of prodromal symptoms, the majority of them subjective, the most important question is whether the patients themselves can recognize their symptoms and predict a forthcoming attack, and thus “treat early” prior to a swelling occurring.

We believe that early signs and symptoms that precede episodes of swelling are potentially helpful and important to further improving the management of HAE. Previously, the information about HAE prodromes has been published in the form of short case reports or series.25–30 Recently, the awareness of the clinical value of prodromes increased the number of more purposeful clinical research studies involving larger cohorts of patients.24,31–34 In 2013, Reshef et al. gathered the results from 3 independent surveys (totalling 113 patients) conducted in Israel and the USA, thus providing the largest source of data at that time.16 The study showed that the majority of patients (83–96%) reported experiencing prodromes and 2/3 indicated that prodromes preceded > 50% of their attacks. Furthermore, prodromes are experienced in 42–58% of paediatric HAE patients.28,35 More recently, in a survey conducted in 2019, 84% of patients declared ever experiencing a prodrome and 64.3% confirmed that they could predict an oncoming attack.21,31 All this data is in agreement with the results delivered by our study. We conducted one of the largest surveys of its kind by simultaneously collecting data from 208 HAE patients from the UK and Spain. The results demonstrated that 56% of patients who had ever experienced a prodrome were usually aware of prodromal symptoms before the swelling occurred.

Previous studies by Leibovich et al. indicated there was a significant correlation between the perception of prodrome and the ability of patients to predict an oncoming attack.21 Our survey confirmed that for most patients, the early signs have a predictive nature, allowing them to be aware that an attack is underway and that swelling may be imminent, and to prepare for it. Interestingly, the actions taken by patients when they experienced prodromal signs differed between the UK and Spain. While the majority of patients in the UK (56%) reported taking some form of medication and 2/3 indicated that prodromes preceded > 50% of their attacks. Furthermore, prodromes are experienced in 42–58% of paediatric HAE patients.28,35 Of those participants who took medication when they had prodromal symptoms before the swelling started, two-thirds felt that they had avoided an attack by treating early. Importantly, the percentage of patients who only needed one injection to treat the attack increased when patients took their medication early in the prodromal stage (from 55 to 66%). Although the medication injected by the patients was not specified, we suspect that it was most likely icatibant, given the known half-lives of the various products. These findings suggest that early self-treatment does improve
treatment response. This is consistent with the evidence in the literature showing that early treatment is associated with a shorter time to symptom resolution and shorter total HAE attack duration, regardless of attack severity.\textsuperscript{20,36} However, the specificity of prodromes is still unknown and treating early may lead to overuse of on-demand therapy.\textsuperscript{21,24,31,37}

Of note, the 2021 international World Allergy Organization (WAO)/European Academy of Allergy and Clinical Immunology (EAACI) HAE guidelines advocate treating all attacks as early as possible.\textsuperscript{37} The recommendations are based on studies showing that early on-demand treatment of HAE attacks with intravenous-C1-INH, ecallantide, or icatibant provides a better treatment response than late treatment.\textsuperscript{20,38–40} Most significantly, the guidelines acknowledge that in many patients, a significant number of attacks are preceded by prodromal symptoms, and in some, this may be an opportunity to treat before an attack occurs.\textsuperscript{37}

Our survey data does indicate that a considerable proportion of patients do already use treatment in the prodromal phase.

Although almost three-quarters of respondents said that their HCP had advised them to ‘treat early’, the understanding of what is meant by ‘treat early’ is variable, with some patients believing that this means taking the medication as soon as the swelling starts. 39% of participants take their medication at the prodromal signs, but 50% wait for the swelling to start. Given the pain associated with the attacks, the aim would be to treat as soon as prodromes occur, not only to reduce the duration and severity of the attacks but, more crucially, to prevent swelling altogether. Further studies are therefore needed to determine the percentage of attacks that are preceded by prodromes and to show the relationship between prodromes and attacks. This is of paramount importance, especially in light of recent evidence showing that pathophysiological changes begin as early as the onset of EM, suggesting that the prodrome is not a separate entity but actually a first phase of an attack itself.\textsuperscript{17}

Our study has several limitations related to survey methodology, such as population bias (patients who accepted the invitation were self-selected), recall bias, and potential misclassification of responses. In addition, the survey excluded patients under the age of 16 years and therefore does not reflect the paediatric population. Response to the study was voluntary and the validity of the results is limited to the population that completed the survey. These limitations restricted our analysis to a descriptive presentation of the findings. However, the fact that the results were generally consistent with published literature indicates that these limitations did not overly bias the results.

Conclusions

In summary, we show that in our large sample of patients with early symptoms, the majority can always or usually predict an impending swelling and that treatment at an early stage is associated with better outcomes. These results add to the growing body of data on this topic although further research is still required. HAE patients continue to face a number of difficulties and this highlights the need for more focused, well-designed studies in this area to better characterize prodromal signs and symptoms, their predictive value, and the temporal relationships between prodromes and attacks. We hope that our findings will stimulate further interest in how prodromes can contribute to management of HAE. Better characterization and understanding of prodromal symptoms may help patients recognize that an attack is developing and institute preventative behavioural or treatment measures to mitigate swellings and lessen the impact of the disease on their day-to-day life.

References


**Figure legends**

**Figure 1** Types of prodromal signs and symptoms experienced by HAE patients (*N*=208). Data is expressed as percentage.

**Figure 2** First actions taken by patients when prodromal signs/symptoms start (*N*=208). Data is expressed in numbers of participants.

**Figure 3** Frequency of medication intake by patients experiencing early signs/symptoms before onset of swelling (*N*=208). Data is expressed as percentage.

**Figure 4** Time medication was taken by patients after the onset of a prodrome symptom (*N*=122). Data is expressed as number of participants who took medication in the prodromal period. *Note. All responders who took medication before the swelling started.*

**Figure 5** Number of injections used to treat HAE attack. (5A) Number of injections that patients usually needed to treat an attack (*N*=202). (5B) Number of injections that patients needed to treat an attack if they experienced a prodrome and took medication before the swelling started (*N*=117). Data is expressed as percentage. *Note. All responders who were not taking only danazol or berotralstat.*

**Figure 6** Patient understanding of the meaning of ‘treat early’ (*N*=146). Data represent patients that were advised to treat early by health care professionals and is expressed as % of participants.

**Hosted file**