Characterization of prodromal symptoms in a large population of patients with hereditary angio-oedema

M. Magerl,1 G. Doumoulakis,1 I. Kalkounou,1 K. Weller,1 M. K. Church,1 W. Kreuz2 and M. Maurer1
1Department of Dermatology and Allergy, Charité–Universitätsmedizin Berlin, Berlin, Germany; and 2HZRM Hämostase-Zentrum Rhein Main, Mörfelden-Walldorf, Germany

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Summary

Background. Hereditary angio-oedema (HAE) due to C1-inhibitor (C1-INH) deficiency is a rare autosomal dominant disease. It predisposes affected patients to attacks of disfiguring, painful angio-oedema, which, in cases of involvement of the upper airways, can be life-threatening. Frequently, prodromal symptoms occur hours to days before an attack, but their predictive value is uncertain.

Aim. To characterize the spectrum of prodromal symptoms in patients with HAE in Germany.

Methods. A questionnaire asking about the frequency, type and time of occurrence of prodromal symptoms, and the interval until the onset of an attack of HAE was sent to 808 German patients with HAE. Answers from 365 participating patients were analysed.

Results. The survey showed that 79% of patients with HAE had experienced ≥ 1 prodromal symptom before an attack of angio-oedema. The most commonly reported prodromal symptoms (67% of which occurred within 6 h before an attack) were fatigue, malaise and short temper. Significantly more women than men reported having prodromes (83% vs. 73%, P < 0.05). Over 90% of the patients with prodromes reported that they were able to predict the onset of an attack with a certainty of ≥ 50%. In addition, there was a significant correlation between the occurrence of skin rashes and delay in the diagnosis of HAE.

Conclusions. The results of this survey may aid the management of C1-HAE by recognizing that prodromal symptoms are of value in predicting the onset of an attack of angio-oedema and in diagnosing the condition.

Introduction

Hereditary angio-oedema (HAE) due to C1-inhibitor (C1-INH) deficiency is a rare autosomal dominant inherited disease, with an estimated prevalence of 1 : 50 000 in the general population.1,2 HAE can be caused by a quantitative (HAE-I) or qualitative (HAE-II) deficiency of C1-INH. C1-INH is the main regulatory protein of proteases of the plasma kallikrein–kinin system.3 Reduced C1-INH activity results in increased activation of plasma kallikrein–kinin system proteases, resulting in raised bradykinin levels. Local increase in bradykinin levels leads to a rise in vascular permeability, followed by plasma extravasation into the intersti-
tial space, thus leading to the onset of angio-oedema symptoms.4

Clinically, C1-HAE is characterized by self-limiting attacks of nonpitting, nonpruritic swelling of the skin and subcutaneous tissues, and attacks of mucosal swelling. The angio-oedema may occur in variable degrees of severity, and it is often localized to one or several locations of the body including the limbs, genitalia, face, oropharynx, tongue, laryngeal tissues, torso and visceral organs.2,5,6 Because of its significant morbidity and mortality of 15–30% due to untreated or insufficiently treated laryngeal oedema and subsequent asphyxiation, all patients need to carry emergency therapies, and some require long-term prophylaxis.7–9

Numerous reports about prodromal signs and symptoms of C1-HAE attacks have been reported in the literature, including in the first descriptions of HAE by Dinkelacker and Quincke over 130 years ago.10–15 Quincke described malaise as a prodrome,11 while Dinkelacker10 reported a preceding ‘red and marbled condition of the skin of the breast’ in two patients from one family, and he was also the first to mention short temper as a prodrome. Prodromes develop minutes to hours before the onset of the actual angio-oedema episode. Not all patients develop prodromes, and not all patients who do develop prodromes do so for every attack. In addition, the spectrum of prodromes varies both between and within individuals. A better understanding of the frequency, predictive value and timing of prodromes might help to optimize on-demand treatment, which works best when given before or early in an attack.16–18

The purpose of this survey was to review the prodromal signs in a large series of patients with HAE in Germany, and to assess their frequency, type and time of occurrence, and the interval until the onset of an attack.

Methods

An extended questionnaire was sent in June and July 2008 to 808 patients with HAE, representing approximately 50% of the known German HAE patient population. The questions covered epidemiology, triggers, prodromes, symptoms and therapy.

The questionnaires were sent to the patients by the German patient organization HAE Vereinigung e.V (Aachen, Germany). The questionnaire was developed in collaboration with the HAE Vereinigung e.V. and PSYMA International Medical Marketing Research GmbH (Ruckersdorf/Nuernberg, Germany), and supported by CSL Behring GmbH (Hattersheim, Germany).

Patient anonymity was secured in accordance with German data protection law. Patients were requested to retrospectively complete the questionnaire and return it anonymously.

Statistical analysis

As the data were not normally distributed, statistical comparisons were made using the Mann–Whitney U-test.

Results

Demographics

Of the 808 patients with HAE who received a questionnaire, 365 patients (45%) returned a completed questionnaire, and all of these were eligible for statistical analysis. The 365 patients comprised 126 male patients (median age 47 years, range 14–80) and 239 female patients (median age 44 years, range 8–83). Most of the patients had developed the condition early in life; 92% before the age of 25 years (Fig. 1). The median age of onset of HAE symptoms was 14 years (range 1–78) in male patients and 12 years (range 1–65 years) in female patients.

Prodromes

The occurrence of at least one prodromal symptom before the onset of an HAE attack was reported by 290 patients (79%). Prodromes were more often described by patients with frequent attacks; in the pop-

![Figure 1](https://via.placeholder.com/150)
ulation with no prodromes, 39% had < 6 HAE attacks per year (median number of attacks per year: 7), whereas only 16% of the patients with prodromes had < 6 attacks per year (median: 24), and this difference was significant (P < 0.01). The most common prodromes reported were fatigue (75%), malaise (74%) and short temper (72%). Other common prodromes were skin rashes (65%), restlessness (52%) and sadness (37%). Other less common prodromes, (each reported by < 5% of patients) included stomach and gut problems (flatulence, nausea/vomiting or abdominal pain), dysaesthesias (numbness, tingling, tenseness) and itching in various locations of the body (hands, thumbs, canthus). Pain in the extremities and sensation of thirst were rare prodromes, experienced by < 1% of patients.

Significantly more female than male patients reported that they experienced prodromes (83% vs. 73%; P < 0.05). Furthermore, the frequency of fatigue, malaise, short temper and sadness, but not skin rashes and restlessness, were significantly more common in female than in male patients (Fig. 2).

**Prodromes as predictors of an attack of hereditary angio-oedema**

When asked if their prodromes were followed by HAE attacks, 243 respondents gave more detailed information: 220 patients (91%) stated that this was the case on 50% of occasions, with 52 patients (21%) reporting that the occurrence of prodromes was followed by an attack on ≥ 95% of occasions. Only 23 patients (8%) indicated that less than half of their prodromes were followed by an attack (Fig. 3).

In more than two-thirds of the patients, prodromes occurred < 6 h before the onset of an attack (Fig. 4). Delays of longer than 24 h were rare. There was no correlation between the duration of delay and the certainty of prediction.

**Prodromes and diagnosis of hereditary angio-oedema**

There was a considerable delay between onset of symptoms and the correct diagnosis being obtained: the median time in our population of 365 patients was 9 years (range 0–64). The occurrence of skin rashes as a prodromal symptom appeared to delay the diagnosis of HAE to a median of 11 years compared with 7 years for patients who never displayed any prodromal skin rashes. This difference was highly significant (P < 0.005, Mann–Whitney U-test).
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Discussion

In this survey of 365 patients with C1-HAE, we found that 79% had at least one prodrome before onset of an acute attack. These numbers are in line with the figures of 82.5–95.7% reported for the three surveys of Reshef et al.19 The primary findings in the current study were that the most commonly reported prodromal symptoms were fatigue, malaise and short temper; that most prodromes occurred within 6 h before an attack; and that > 90% of the patients with prodromes could predict the onset of an attack with a certainty of ≥ 50%.

Fatigue and malaise as prodromes have frequently been reported in the literature.11–15,19 Prematta et al.14 reported that 29 of 44 patients with prodromes experienced unusual fatigue before their most recent attack. The options in our questionnaire of short temper, sadness and restlessness have been described in other publications,19 by slightly different terms, such as depression, irritability, discomfort change in affect/energy and others. Lack of a clear definition and the low specificity of these terms make studies difficult to compare. However, it seems that these kinds of emotional disturbances are more frequent in our population compared with other HAE populations in the literature.20

Our finding that 67% of prodromal symptoms occurred within 6 h before an attack is different to the two papers of Prematta et al. In their first paper, they stated that 55% of their patients reported the onset of prodromal symptoms > 24 h before C1-HAE symptoms developed, while in the remaining 45%, the interval was < 12 h.14 The second paper reported a median time of 12 h between the onset of prodrome and the onset of angio-oedema symptoms.15 The reason for this difference is unknown.

In the questionnaire, > 90% of the patients with prodromes stated that they could predict the onset of an attack with a certainty of ≥ 50%. These figures are somewhat higher than those reported by Prematta et al.,14 who reported that only 65% of their patients believed they could predict an attack with a certainty of ≥ 50%. Furthermore, 21% of our patients stated that their prodromes were followed by an attack in ≥ 95% of cases. This figure is lower than that found in a survey of Reshef et al.,20 in which about two-thirds of participants reported experiencing prodromes before all or most of their acute HAE attacks. Unfortunately, our database did not allow us to assess the data for differences in certainty of prediction between the different types of prodromal symptoms. It would be interesting, for example, to investigate whether objective prodromes, such as erythema marginatum, have a higher predictive value than subjective symptoms such as fatigue or sadness.

Because C1-HAE is an autosomal dominant inherited disease, both sexes should be similarly affected. However, women appear to have a more severe course of disease than men.6 This was supported by our study, with women reporting prodromal symptoms, particularly fatigue, malaise, short temper and sadness more often than men.

We found a significant correlation between the occurrence of skin rashes and delay in diagnosis of HAE. Skin rashes were first described as prodromes in HAE by Dinkelacker in 1882,10 and have been repeatedly reported since then, although their descriptions have been somewhat variable. In 1973, Starr and Brasher21 compiled some terms that could be used to describe or diagnose the rashes, including ‘red rings’, ‘erythema multiforme’, ‘serpiginous erythema’, ‘diffusely mottled’, ‘macules’ or ‘welts’. Even so, prodromal rashes have often been mistaken for urticarial weals, leading to misdiagnosis. Indeed, Farkas et al.12 described three cases of patients in whom erythema marginatum was thought to result from an allergic pathomechanism, and corticosteroid therapy was initiated, resulting in a delay of many years in obtaining the correct diagnosis.

The primary strength of this survey was the large number of patients who completed the questionnaire. However, such patient-completed questionnaires also have inherent weaknesses. These include the retrospective nature of the study and that mainly adult patients responded; only 12 patients were younger than 18 years. Further more, because the questionnaire was handed to the patients by the national patients’ organization, we cannot be sure whether patients with diagnoses other than C1-HAE also completed the questionnaire. For example, 22 patients (6%) reported that they began to have symptoms after the age of 40 years. Late onset of symptoms is extremely unusual with C1-HAE6 but is associated with acquired angio-oedema due to C1-INH deficiency (AAE-C1-INH), whose symptoms are very similar to C1-HAE.22

Conclusion

In this study, we found a very high predictive value of prodromes in > 20% of patients with C1-HAE, and a good predictive value of ≥ 50% in almost 70% of patients. The high certainty of the patients in predicting attacks based on prodromes indicates that prodromes could be used as an indication for treatment in some patients. Early treatment is more effective, and thus is recommended by the WAO guideline.1,16,17
A clinical study is warranted to assess the clinical usefulness and cost-effectiveness of the implementation of specific treatment when prodromal symptoms occur, rather than at the onset of an angio-oedema attack.

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What’s already known about this topic?

• The occurrence of prodromal signs and symptoms of hereditary angio-oedema due to C1-esterase inhibitor deficiency (C1-HAE) has been reported for > 30 years.
• These symptoms may be rather specific in nature, such as erythema marginatum, or non-specific, such as paraesthesia, tingling, stinging, fatigue, muscle aches and malaise.
• Systematic data collection on prodromes is rare, making it difficult to assess their value in predicting the onset of attacks of angio-oedema or in aiding diagnosis.

What does this study add?

• This questionnaire study of 365 patients with C1-HAE found that 79% had experienced ≥ 1 prodromal symptom, occurring most commonly within 6 h before the onset of oedema symptoms.
• The results of this study should aid in the management of C1-HAE by recognizing that prodromal symptoms are of value in predicting the onset of an attack of angio-oedema and in diagnosing the condition.

References

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