

Per-Attack Reporting of Prodromal Symptoms Concurrent with C1-Inhibitor Treatment of Hereditary Angioedema Attacks

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ABSTRACT

Introduction: Prodromal symptoms commonly precede hereditary angioedema (HAE) attacks. There is continuing interest in evaluating prodromes as treatment indicators, but a paucity of relevant data. This study was designed to prospectively identify prodromal characteristics in patients voluntarily reporting such information around the time of seeking treatment for an acute HAE attack.

Methods: Twenty-eight patients with HAE were enrolled in this survey, which was conducted in the context of an open-label study of treatment

of HAE attacks with plasma-derived C1-inhibitor concentrate. At the time of treatment, patients were encouraged to answer survey questions about prodromal symptoms preceding that particular HAE attack.

Results: Twenty-one patients provided prodromal information for 253 treated HAE attacks. Seventy-one percent of patients (15/21) reported prodromes. Three patients accounted for approximately 80% of the attacks and 89% of the reported prodromal symptoms. Prodromes were experienced before 67.6% (171/253) of attacks, with a mean of 1.4 prodromes per attack. Fatigue was the most

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frequent prodrome (42% of attacks), followed by nausea (26%), and flu-like symptoms (22%). The median duration of a prodrome before an attack was 12 h (range, 0.33–24 h).

Conclusions: Despite many limitations in the study design, these findings confirm that prodromes are frequently associated with HAE attacks in many patients and occur sufficiently early to allow time for treatment initiation. The frequency of “false positive” prodromal symptoms remains undetermined, and the authors captured data only on attacks severe enough to warrant treatment. Additional well-designed prospective studies are clearly needed to continue investigating the potential clinical relevance of prodromes.

Keywords: C1-esterase; C1-inhibitor deficiency; Fatigue; Flu-like symptoms; Hereditary angioedema; Nausea; Plasma-derived C1-inhibitor; Prodromal symptoms; Prodromes

INTRODUCTION

Hereditary angioedema (HAE) is a rare (prevalence of only 1:10,000 to 1:50,000 people) autosomal dominant disorder that is generally marked by a functional or quantitative deficiency of C1-inhibitor (C1-INH), a serine protease inhibitor that is a major mediator of vascular permeability [1, 2]. Affected individuals experience recurrent episodes of nonpruritic, nonpitting edema that are often localized to the abdomen, extremities, bowels, genitalia, chest, face, tongue, pharynx, or larynx [1]. Severe attacks can cause substantial pain and deformity and, in the case of upper airway symptoms, can be life-threatening [3]. The primary management goals of HAE are to prevent attacks and to terminate attacks soon after they occur [4]. A purified, human-plasma concentrate formulation of

C1-INH has been used for the treatment of HAE in Europe and elsewhere for more than two decades [5]. In a recent multinational study, the International Multicenter Prospective Angioedema C1-Inhibitor Trial 1 (I.M.P.A.C.T.1), Craig et al. reported the efficacy and safety of the C1-INH concentrate, which was approved in 2009 by the US Food and Drug Administration for the treatment of acute HAE attacks [6]. Other agents approved in the US for the prophylaxis or treatment of HAE in recent years include a plasma-derived C1-INH concentrate, which was approved in 2008 for prophylaxis of HAE attacks in adolescents and adults; the kallikrein inhibitor ecallantide, approved in 2009 for acute attacks of HAE; and the bradykinin receptor antagonist icatibant, approved in 2011 for treatment of acute attacks in adults ≥ 18 years of age [7–9]. A recombinant human C1-INH product was recently approved for use in the European market and remains under development in the US.

HAE attacks are often, but not always, heralded by prodromal symptoms that alert the patient to an impending episode. Common prodromal symptoms include unusual fatigue, rash, muscle aches, abdominal pain, and nausea [4]. Only a small amount of data has been published about prodromal symptoms and their characteristics and potential predictive significance remains unclear [10]. Most of the available literature comprises case reports, small case series, or retrospective surveys that are prone to recall or self-selection bias [4, 11–19]. A better understanding of the potentially predictive nature of prodromal symptoms would therefore be of great value for the timely detection of impending attacks and for designing strategies for rapid attenuation or deterrence of HAE attacks [10].

An extension of I.M.P.A.C.T.1 was designed to assess the real-world impact of human-plasma

concentrate formulation of C1-INH for HAE attacks. This extension study (I.M.P.A.C.T.2) was a long-term (2006–2010), prospective, open-label, uncontrolled, phase 3 study of the C1-esterase inhibitor Berinert® (CSL Behring GmbH, Marburg, Germany) for acute HAE attacks at 14 centers in the US and one center in Canada [20]. The authors report the results of a survey, the Companion Survey for Subjects With Congenital C1-INH Deficiency Enrolled in the phase 3 Open-label Extension Study of Human Pasteurized C1 Esterase Inhibitor Concentrate, of prodromal symptoms conducted in a subgroup of patients from I.M.P.A.C.T.2. Subjects were encouraged to report the presence or absence of prodromal symptoms as an optional survey component when they experienced a HAE attack and received C1-INH treatment, a design which was expected to limit the potential for recall bias compared to retrospective surveys. In most instances, subjects completed the prodrome questionnaire within 48 h of the event. The survey also included components soliciting patient feedback on their personal and family HAE history and treatment outcomes related to their current attack, neither of which are discussed in this paper.

METHODS

Patients who participated in this optional companion study to I.M.P.A.C.T.2 were ≥ 6 years of age, with a laboratory-confirmed diagnosis of type 1 or type 2 HAE. The study protocol was approved by Mid*Land Institutional Review Board (Leawood, Kansas, USA), and all patients or their legal representatives provided written informed consent.

Patients in the I.M.P.A.C.T.2 study were eligible for treatment with 20 U/kg of C1-INH at the onset of HAE attack symptoms without restriction on body location. At the time of treatment, patients

Table 1 Prodromal symptoms survey questionnaire, completed in conjunction with each attack treated with C1-inhibitor

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1. Did you have prodromal symptom(s) before this attack?
 2. If yes, what type of prodromal symptom(s) did you have?
 - Tingling
 - Fatigue
 - Nausea
 - Abdominal rumbling
 - Bowel movement change
 - Flu-like feelings
 - Hives
 - Non-itchy rash with pale centers
 3. If yes, where did you experience the prodromal symptoms prior to the attack?
 4. If yes, what was the duration of the symptom(s) before the attack?
-

were encouraged to answer survey questions relevant to the nature and duration of any prodromal symptoms experienced before the current attack. The questionnaire was designed to be self-completed, thus employed patient-friendly terminology (Table 1). As part of the survey development process, the authors conducted a small pilot study which employed a questionnaire with multiple open-ended questions; the final questionnaire was designed and validated based upon the pilot study responses, with input from a team of biostatistical experts and professional survey developers. “Duration” of prodrome was defined as time from onset of prodrome to onset of the attack itself. This interval is considered of most relevance for determining if prodromal symptoms might provide a logical timeframe within which to initiate treatment. Responses were transmitted via home computer or interactive telephone voice-response service to a central, computerized database (Clarix™ Informatics, Princeton, New Jersey, USA). Data were sought about the type and location of the prodromal symptom(s), the number of attacks

preceded by a prodrome, symptom duration before onset of the HAE attack, the most frequent combinations of prodromal symptoms, and the site of the attack. Responses were compiled and analyzed using descriptive statistics only.

RESULTS

Twenty-eight patients (mean age, 34.9 years; range, 13–56 years) from seven sites in the US were enrolled between January 2007 and September 2009 in this open-label survey study of C1-INH for acute HAE attacks (a total of 57 patients [mean age, 31.9 years; range, 10–53 years] participated in the I.M.P.A.C.T.2 clinical study). Twenty-one patients provided prodromal information for 253 attacks that were treated with C1-INH.

The most common location of a HAE attack was the abdomen (68.8% of attacks), followed by the extremities (18.6%), larynx (4.7%), face (1.6%), genitourinary area (1.6%), and other body sites (4.7%). In total, 15 of 21 patients (71%) reported prodromes. Prodromal symptoms were experienced before 171 of the 253 (67.6%) attacks, with an absence of any prodrome (“none”) indicated in the remaining 82 attacks (32.4%) (Table 2). A total of 355 individual prodromal events were reported, with an average frequency of 1.4 prodromal symptoms per treated attack.

Five subjects accounted for >85% (224 of 253 attacks) of the reported HAE attacks. Within this subgroup, 34.4% to 98.2% of attacks were characterized by at least one prodromal symptom (range, 0–6 prodromes per attack). The overall mean number of prodromal symptoms per treated HAE attack in these five patients was 1.5. In order to determine if the high frequency of attacks and prodromes in these three patients was skewing the results, the authors determined prodrome frequencies for the population with those three patients removed. The results of this analysis can

be seen in Table 2, indicated in italics below the values for the entire population. The pattern of prodrome events did not appear to be markedly different after removing the three outlier patients. Among abdominal attacks, which were the most frequently reported, the incidence of some of the more vague prodromal symptoms such as fatigue, nausea, and flu-like symptoms was higher among the three outlier patients.

Considerable variability was seen in the pattern of prodromes preceding attacks. For example, one patient reported 20 unique prodromes or combinations over the course of 83 treated attack episodes, and another patient reported eight unique prodromes or combinations associated with 16 attacks. The types of combination symptoms occurring in one attack also varied considerably among patients. Fatigue was the prodromal symptom most frequently seen in combination with one or more other symptoms. Fatigue and nausea occurred together before 52 attacks; however, 45 of those combinations were seen in one patient, and in 41 of those attacks, fatigue and nausea were accompanied by flu-like symptoms. Other symptoms seen in combination with fatigue included non-itchy rash with pale centers (before 12 attacks in two patients), bowel movement change (nine attacks in three patients), hives (six attacks in one patient), and abdominal rumbling (five attacks in two patients).

Fatigue, reported in 42% of attacks, was the most frequently described prodrome. Nausea and flu-like symptoms were reported in 26% and 22% of attacks, respectively. There were 28 reported prodromes of hives occurring in various locations: feet ($n = 7$), hands ($n = 6$), chest ($n = 4$), face ($n = 2$), back ($n = 2$), abdomen ($n = 1$), and other ($n = 6$). Non-itchy rash with pale centers was reported on the back ($n = 11$), chest ($n = 9$), hands ($n = 4$), abdomen ($n = 1$), feet ($n = 1$), and other areas ($n = 2$). Attacks labeled as “other” were localized to the

Table 2 Distribution of prodromes within various hereditary angioedema (HAE) attack site categories

HAE attack sites		Prodromes, <i>n</i> (%)									
		Fatigue	Nausea	Flu-like symptoms	Non-itchy rash	Hives	Bowel movement change	Rumbling	Tingling	Other	None
Abdominal	<i>n</i> = 174	96 (55.2)	64 (36.8)	53 (30.5)	19 (10.9)	20 (11.5)	20 (11.5)	16 (9.2)	8 (4.6)	9 (5.2)	37 (21.3)
	<i>n</i> = 40	6 (15.0)	4 (10.0)	2 (5.0)	0	1 (2.5)	2 (5.0)	3 (7.5)	5 (12.5)	1 (2.5)	17 (42.5)
Extremities	<i>n</i> = 47	3 (6.4)	0	1 (2.1)	3 (6.4)	2 (4.3)	2 (4.3)	2 (4.3)	1 (2.1)	6 (12.8)	33 (70.2)
	<i>n</i> = 17	0	0	0	3 (17.6)	0	1 (5.9)	0	1 (5.9)	0	12 (70.6)
Laryngeal	<i>n</i> = 12	4 (33.3)	1 (8.3)	2 (16.7)	3 (25.0)	2 (16.7)	0	1 (8.3)	0	2 (16.7)	1 (8.3)
	<i>n</i> = 2	1 (50.0)	0	0	1 (50.0)	0	0	0	0	0	0
Facial	<i>n</i> = 4	0	0	0	0	0	0	0	0	1 (25.0)	3 (75.0)
	<i>n</i> = 2	0	0	0	0	0	0	0	0	1 (50.0)	1 (50.0)
GU	<i>n</i> = 4	1 (25.0)	0	0	0	1 (25.0)	1 (25.0)	0	0	0	1 (25.0)
	<i>n</i> = 1	0	0	0	0	0	1 (100.0)	0	0	0	0
Other	<i>n</i> = 12	2 (16.7)	1 (8.3)	0	1 (8.3)	3 (25.0)	0	0	1 (8.3)	1 (8.3)	7 (58.3)
	<i>n</i> = 3	1 (33.3)	1 (33.3)	0	1 (33.3)	0	0	0	1 (33.3)	0	0

Values in italics in each cell represent outcomes for the population minus the three patients with the highest frequency of attacks/prodromes, for comparison. Data report the number of prodromes by type preceding attacks by location. Numbers in parentheses represent the percentages of HAE attacks within each site category associated with a given prodromal type

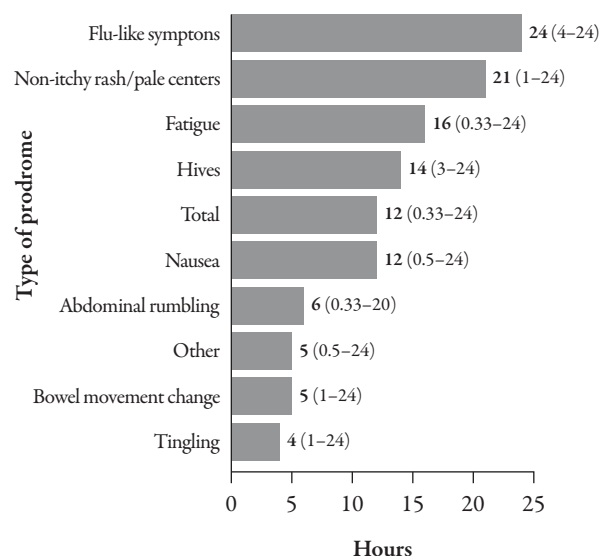


Fig. 1 Median time, h (range) between the onset of a prodromal symptom and the onset of a hereditary angioedema (HAE) attack

abdominal ($n = 6$), extremity ($n = 7$), genitourinary ($n = 2$), laryngeal ($n = 2$), facial ($n = 1$), or other ($n = 1$) body locations.

The duration of a prodromal symptom before a HAE attack (i.e., the time between the onset of a prodrome and the appearance of attack signs and symptoms), ranged from 0.33 h to 24 h (Fig. 1). The median duration for all symptoms combined was 12 h. The median duration for individual symptoms was longest for flu-like symptoms (24 h), rash (21 h), and fatigue (16 h). Bowel movement changes and tingling were associated with the shortest median durations (5 h and 4 h, respectively).

Table 2 shows the number and type of prodromes associated with HAE attacks by site. Fatigue was the most consistent prodromal symptom for abdominal attacks, reported in 55.2% of attacks (96 fatigue prodromes preceded 174 abdominal attacks). Nausea and flu-like symptoms were experienced before about one-third of abdominal attacks. Approximately one-fifth of abdominal attacks were not

associated with any prodromal symptoms. HAE attacks localized to the extremities were most frequently reported as having no prodromal events (70.2%).

Odds ratios were calculated for the likelihood for a specific type of attack to be preceded by a prodrome versus the likelihood of all other attacks to be preceded by prodromes. The odds ratio that an abdominal attack would be preceded by a prodrome compared to all other attacks combined was 7.42; the odds ratio for an extremities attack compared to all other attacks combined was 0.09; and the odds ratio for a laryngeal attack compared to all other attacks combined was 4.07. No statistical comparisons were made between the odds ratios.

DISCUSSION

HAE is a debilitating disease that causes significant physical and emotional morbidity [21]. Not surprisingly, there has been a high level of dissatisfaction among patients with HAE in the US about management of the disease [22], due largely to the lack of an approved, highly effective treatment until late 2009. Now that three specific, efficacious therapies have been approved, new treatment strategies may be evaluated to further reduce the burden of this disease on health-related quality of life, mental health, and productivity. The approach the authors have taken is to obtain a better understanding of the occurrence of prodromal symptoms preceding an acute HAE attack as well as to explore the time relationship to the attack. The authors hope that this information is useful for the design of new treatment protocols that would explore the benefits of initiating treatment based on prodromal symptoms in HAE patients.

The study reported in this paper is one of the first prospective assessments of HAE prodrome

frequency, type, and duration, and not a retrospective questionnaire subject to recall bias. Patients reported prodromal symptoms on an attack-by-attack basis throughout the study period which should have minimized the risk of recall bias. Short-term recall bias was still possible, given that patients may have responded to the questionnaire within many hours following the prodrome experience. In most cases, this time window was <48 h. It is also possible that the physical discomfort and emotional stress associated with a HAE attack could have hindered patients' abilities to respond accurately to the questionnaire. Data collection was also designed to be user-friendly. For example, prodromal skin manifestations were entered as "hives" rather than as a medical term such as erythema marginatum. The pilot study used to develop the questionnaire noted that patients frequently used the term "hives" when asked open questions about prodromes. For this reason, this term was included. The authors suspect that in most cases, patient-identified "hives" were actually erythema marginatum. We acknowledge that patient-friendly terminology has a trade-off of lessening the scientific merit of the findings; future studies of this type might benefit from more clearly-defined symptom definitions.

Most patients providing prodromal feedback reported between one and five attacks during the course of the study, with a range of one to 83 attacks among these patients. Abdominal attacks constituted two-thirds of the HAE attacks, with attacks in the extremities accounting for almost one-fifth of all attacks. A majority of patients experienced prodromal events before attacks, although there was great interpatient variability in the number, types, and sites of prodromes. Two-thirds of all attacks were preceded by prodromes; on average, each attack was preceded by 1.4 prodromal events.

Fatigue, nausea, and flu-like symptoms were the most commonly reported prodromes overall (associated with 22–42% of attacks). Fatigue was also the prodrome that most often preceded abdominal attacks. Laryngeal attacks, posing the greatest risk of morbidity, were rare in this study, and were preceded by prodromes in all but one instance. In a qualitative analysis, when the odds ratios for the three most common sites of attacks were compared, abdominal attacks were almost twice as likely as laryngeal attacks to be preceded by prodromes, while extremity attacks were the least likely to be associated with prodromes. The duration of prodrome onset before a HAE attack ranged from 0.33 h to 24 h, with a median duration of 12 h for all prodromes.

The results of this study corroborate the systematic literature review by Kemp and Craig [10], and a recent retrospective study by Premetta et al. [4]. Consistent findings from the two reports are that skin manifestations (e.g., rashes, hives, or erythema marginatum) and feelings of unusual malaise or fatigue are among the most common types of prodromes preceding HAE attacks. Other prodromes identified in both reports include muscle aches, sensations of numbness or tingling at the sites of future attacks, and upset stomach or nausea [4, 10].

Likewise, the trends reported in the Prematta et al. study [4] are consistent with the results of our study. For instance, both studies showed that prodromes occur before 68% to 87% of HAE attacks. Differences between the two studies may be accounted for by the variation in the types of prodromal symptoms solicited in the two surveys. Furthermore, the Prematta et al. study [4] and previously reported studies reviewed in Kemp and Craig [10] were retrospective, with the possibility of recall bias. For this reason, this study was designed to query patients at the time of treatment of attacks, generally within hours of prodrome symptom onset. A major limitation

of the generalizability of the findings is the fact that 80% of the prodrome data were supplied by only three patients. When the authors compared these three patients to the entire cohort minus these three there were no suggestions that they distorted the results (Table 2). The large proportion of attacks in a small number of patients reflects the difficulty of generating large quantities of data about a relatively rare disease with variable attack frequency. Despite this limitation, these are presently the best data available on prodromes, and for this reason may be useful in the design of future studies to determine if treatment at the onset of prodrome is effective at limiting attacks, if it is cost effective to treat at onset of prodromes when direct and indirect costs are compared, and to determine the specificity of prodrome symptoms. The data suggest that prodromes are sensitive markers of an impending attack, but the authors did not attempt to determine specificity.

The median duration of prodromes in this study was 12 h, suggesting that patients would likely have sufficient time to obtain early treatment following prodromal onset, especially with the emerging possibility of home-based treatment [23, 24]. This may be especially practical in patients who seem able to predict impending attacks based on prodromal symptoms.

However, pending further research, it remains premature to consider prodromes as treatment indicators. For instance, the authors do not know from this study how often prodromal symptoms resolved without progression to an attack. It is, therefore, possible that treatment at the time of prodromal symptoms may lead to episodes of unnecessary drug administration; however, it would be expected that preemptive treatment at the appearance of suspected prodromal symptoms will lead to less C1-INH usage overall than chronic prophylactic administration. As noted above, the authors also lack data on

the specificity of prodromes as predictors of an attack. Prospective, diary-based studies are required to collect such information. A primary goal of such studies would be the development of validated instruments based on prodromal characteristics that are predictive of attacks. In addition, other studies will be required to determine whether preemptive treatment based on prodromal symptoms alone might reduce the frequency and severity of attacks and the associated morbidity and burden on quality of life.

The authors recognize that the survey methodology has a number of limitations. First, prodrome reporting was solicited only in the event of an attack warranting C1-INH concentrate administration. For these attacks, the authors were able to collect very good information regarding associations between prodrome types and specific attack sites. However, the incidence of assumed prodromal events (e.g., fatigue) that were not followed by an attack was not able to be captured. This information would be of great value in determining the rate of prodrome “false alarms” and the potential cost effectiveness of treating at the prodromal stage. Second, the sample size is small, with 28 enrolled subjects and 21 of these subjects reporting prodromal symptoms. However, HAE is a rare disease, and most clinical studies enroll relatively small numbers of patients compared with studies for more common diseases. For example, 57 patients participated in I.M.P.A.C.T.2, and yet its patient population experienced the largest number of HAE attacks (1,085) treated in a prospective study. Third, the three patients who accounted for approximately 80% of the attacks and 89% of the reported prodromal symptoms had a disproportional impact on the findings. Yet, a comparative analysis of prodromal patterns with these three patients removed did not indicate

major differences in overall patterns. There was generally a lower percentage of reported attacks preceded by no prodrome in the analysis with the three outlier patients removed. It could be that patients with higher overall attack frequencies are more attuned to watching for prodromes, particularly more vague symptoms such as fatigue and nausea. There also exists an interesting possibility of differing inherent disease characteristics, including prodrome frequency, among patients with varying attack frequency. As a final limitation, only attacks treated with C1-INH concentrate were captured and prodromes associated with untreated attacks were not captured. These shortcomings suggest that additional data on the exact specificity of prodromes is needed.

CONCLUSION

The majority of patients who participated in this study experienced prodromal symptoms before HAE attacks severe enough to warrant treatment with C1-INH. The median pre-attack duration of prodromal symptoms was 12 h, suggestive of sufficient time to prepare for and possibly initiate treatment for an attack. While caution should be exercised in interpreting these results and applying them to the overall HAE patient population, the findings add to the growing body of data about prodromes. The authors hope these data will stimulate further research in this area, especially with regard to the sensitivity of prodromes, the effect that prophylactic therapy (both androgens and C1-INH) might have on prodromes, if treatment can be initiated at the first sign of prodrome and be able to prevent an attack, and if it is cost effective to treat prodromes when assessing direct and indirect cost of care. Also, these data may allow future studies to be powered and designed more effectively.

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Conflict of Interest. Dr. Bewtra is a co-investigator for the National Institutes of Health. Dr. Levy is a medical consultant for CSL Behring and Dyax, and is a principal investigator for CSL Behring, Dyax, ViroPharma, Pharming, and Shire. Dr. Wasserman is a consultant for CSL Behring, Baxter, Talecris, an investigator for CSL Behring, and is on the Board of Directors with American Academy of Allergy, Asthma and Immunology (AAAAI). Dr. Machnig is an employee of CSL Behring. Dr. Craig is a speaker for ViroPharma, CSL Behring, and Dyax, a researcher with Dyax, CSL Behring, Shire, and Pharming, and an interest section leader for the AAAAI and a board member of the American College of Allergy, Asthma and Immunology.

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