

Hereditary Angioedema Attacks: Local Swelling at Multiple Sites

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Abstract Hereditary angioedema (HAE) patients experience recurrent local swelling in various parts of the body including painful swelling of the intestine and life-threatening laryngeal oedema. Most HAE literature is about attacks located in one anatomical site, though it is mentioned that HAE attacks may also involve multiple anatomical sites simultaneously. A detailed description of such multi-location attacks is currently lacking. This study investigated the occurrence, severity and clinical course of HAE attacks with multiple anatomical locations. HAE patients included in a clinical database of recombinant human C1-inhibitor (rhC1INH) studies were evaluated. Visual analog scale scores filled out by the patients for various symptoms at various locations and investigator symptoms scores during the attack were analysed. Data of 219 eligible attacks in 119 patients was analysed. Thirty-three patients (28 %) had symptoms at multiple locations in anatomically unrelated regions at the same time during their first attack. Up to five simultaneously affected locations were reported. The observation that severe HAE attacks often affect multiple sites in the body suggests that HAE symptoms result from a systemic rather than from a local process as is currently believed.

Keywords C1-inhibitor deficiency · Hereditary angioedema

Abbreviations

B1R	Bradykinin receptor B1
B2R	Bradykinin receptor B2
C1INH	C1-inhibitor

CRP	C-reactive protein
fC1INH	Functional C1INH
HAE	Hereditary angioedema
HK	High-molecular-weight kininogen
ISS	Investigator symptom score
OFPL	Oro-facial-pharyngeal-laryngeal
RCT	Randomized controlled trial
rhC1INH	Recombinant human C1-inhibitor
TNF	Tumour necrosis factor
VAS	Visual analog scale

Introduction

Hereditary angioedema (HAE) was first described by William Osler in 1888 as a clinical triad of recurrent attacks of local swelling in various parts of the body, often associated with colicky abdominal pain and a dominant hereditary pattern [1]. In 1963 Donaldson and Evans discovered deficiency of the plasma protein C1-inhibitor (C1INH), a major regulator of the bradykinin-forming cascade, as the main pathological defect in patients with HAE [2].

Since its first description, the disease HAE is well described. Though attacks usually evolve at a single anatomical site, the simultaneous occurrence of symptoms at multiple sites have been mentioned [1, 3–10]. In a recent study, 186 HAE patients were interviewed about their last attack. One hundred sixty-four patients had an attack in the previous 6 months, 24 % of them experienced an attack at multiple locations [6]. In another study, 55 % of patients with severe peripheral attacks reported at least two separate anatomical locations of the attack [8]. Likewise a large study evaluating 512 abdominal attacks reported that 51 % of abdominal attacks were associated with symptoms elsewhere [9]. Further, another study observed that symptoms at various anatomical

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sites can develop in a similar fashion and that over the course of an attack, some symptoms can evolve while others emerge [10].

Thus, HAE attacks simultaneously occurring at multiple anatomical sites are frequently mentioned in the literature. However, a detailed description of the clinical manifestations and course of HAE attacks that occur at multiple anatomical locations, further referred to as multi-location attacks, is lacking. The aim of the present study is to evaluate the occurrence, severity, anatomical locations and course of multi-location attacks in a large group of HAE patients.

Patients and Methods

Study Design

This descriptive study is based on a secondary analysis of data from clinical trials with recombinant human C1-inhibitor (rhC1INH) by Pharming Technologies BV, Leiden, The Netherlands. During these trials, an extensive clinical database of more than 100 HAE patients suffering from an acute attack has been made.

Patients

All patients included in this analysis were enrolled in two randomized, double-blind, placebo-controlled trials (RCT) and their open label extensions to evaluate rhC1INH as a treatment for HAE attacks [11, 12]. Patients were asked to fill out a set of visual analog scale (VAS) scores to determine the severity of symptoms during the course of the attack. The VAS forms were designed like a ruler from 0 to 100 mm, 0 indicated no symptoms and 100 mm the most severe complaints possible for the given symptom. The content validity of the VAS instruments used to assess the anatomical locations involved in the angioedema attack and their suitability for patients' assessments of the severity of acute angioedema symptoms have been described elsewhere [13]. For each location, the data collected included the overall severity VAS score and VAS scores designed for specific locations. In addition to the VAS scores, an investigator symptom score (ISS) was collected for each location. Affected locations could be abdominal, oro-facial-pharyngeal-laryngeal (OFPL), genitourinary or peripheral. The exact peripheral location, i.e. left hand or lower back, was described by the physician. Physicians scored the attack on a 0 to 5 scale from no symptoms to life-threatening symptoms. An angioedema attack was eligible for inclusion in the trial when the overall severity VAS score of at least one location of the attack had been rated by the patients as ≥ 50 mm on a 100-mm scale at presentation. A second or third attack location was considered significant when the ISS was ≥ 2 (mild symptoms) or the overall severity

VAS score was rated by the patient ≥ 20 mm at any time point for any additional location. Further, a second location was only eligible when swelling occurred in a clearly distinct anatomical site, i.e. left hand and right hand, but not left foot and left knee. As a part of the clinical protocols, C-reactive protein levels were measured.

Data Analysis

Data not normally distributed are given as the median and range or the interquartile range. Difference in gender and in use of prophylactic medication was evaluated with Fisher's exact test, difference in age and self-reported attacks per year with the Mann-Whitney test. Differences in VAS scores, C-reactive protein (CRP) levels and time interval after a multi-location attack were evaluated with the Mann-Whitney test. The analyses were done with Graph Pad Prism 5 and Microsoft Excel 2003.

Results

Patients Included in the Study

Data from 119 HAE patients suffering from an acute HAE attack were analysed. The average age of the population included was 36 years (SD 14); 43 patients were male and 76 were female. Seventy (59 %) patients used prophylactic therapy for HAE. Androgens were used by 55 (46 %) patients, whereas 11 (9 %) patients used prophylactic C1INH therapy. The median number of historical attacks per year as reported by the patient was 20 (0–150). Functional C1INH levels were below 50 % of normal in all patients and were below the detection limit of the assay in the majority of the patients (Table 1). The median C4 level was 57 $\mu\text{g/mL}$ (range 7.25–320 $\mu\text{g/mL}$, normal range 100–400 $\mu\text{g/mL}$, see Table 1).

Symptoms and Frequency of Multi-location Angioedema Attacks

All 119 patients had at least one eligible angioedema attack; 49 patients had more than one attack during the study period. In total, there were 219 eligible attacks.

Thirty-three of the 119 patients (28 %) had a multi-location attack as their first attack included in the study, i.e. they had symptoms at more than one anatomical location (Table 2). Notably, two patients had an attack involving five anatomical sites. Twenty-nine (88 %) of the 33 multi-location attacks involved at least one peripheral location, most frequently the hands and arms. In 11 (33 %) patients, the multi-location attack only involved peripheral locations. Furthermore, 16 (48 %) patients had abdominal symptoms as part of their

Table 1 Characteristics of the HAE patients included

	Swelling at 1 location	Swelling at >1 location	All patients	<i>p</i> value
Patients (<i>n</i>)	71 (60 %)	48 (40 %)	119 (100 %)	0.698
• Male (<i>n</i>)	16 (37 %)	27 (36 %)	43 (36 %)	0.308
• Female (<i>n</i>)	32 (42 %)	44 (48 %)	76 (64 %)	
• Age (years)	37 (13–71) ^a	35 (16–67) ^a	36 (13–71) ^a	
Prophylactic treatment (<i>n</i>)	41 (58 %)	30 (63 %)	71 (60 %)	0.704
• Androgens (<i>n</i>)	34 (48 %)	21 (44 %)	55 (46 %)	0.710
• C1INH (<i>n</i>)	5 (7 %)	6 (13 %)	11 (9 %)	0.347
Attacks/year (<i>n</i>)	20 (0–150) ^a	24 (3–106) ^a	20 (0–150) ^a	0.435
fC1INH at screening (U/ml)	<28 (<28–60) ^b	<28 (<28–38) ^b	<28 (<28–60) ^b	0.645
C4 at screening (µg/mL)	56 (7.25–320)	69 (7.25–214)	57 (7.25–320) ^a	0.352

^a Median (range)^b Both median and minimum under detection limit of the assay

multi-location attack; 10 (30 %) patients had OFPL symptoms and 6 (18 %) patients had genitourinary symptoms (Table 2).

Forty-nine patients had in total 100 subsequent hospital admissions because of a repeated attack during the study period. The interval between the first and second hospital admission varied from 3 to 562 days with a median interval of 51 days (iq range=22–138). There was no significant difference in the time interval until the second attack after a multi-location or a single location attack ($p=0.382$).

Thirty-four of these 100 (34 %) repeated attacks were multi-location attacks (Table 3). Altogether, 48 (40 %) of 119 patients had a total of 67 multi-location attacks. Combinations of abdominal with peripheral symptoms were with 22 (34 %) cases most reported. There was no difference in age ($p=0.308$), gender ($p=0.698$), use of

prophylactic medication ($p=0.56$) and the number of reported attacks on a yearly basis (median, 20; range, 0–150; p , 0.435) between patients with at least one multi-location attack during the study and patients that had a single affected location (Table 1). Laryngeal involvement was suspected when patients had difficulty breathing (VAS score >20 mm), a changing voice (VAS score >50 mm) and/or difficulty with swallowing (VAS >50 mm). Patients that had a multi-location attack with one location in the OFPL region were not more likely to have laryngeal involvement as part of their OFPL location compared to patients that had OFPL swelling as their only attack location ($p=0.768$).

The frequency of a multi-location attack in the subgroup of 49 patients that had repeated was with 34 % comparable with that of the total study population. In total, the database contained data of 25 subsequent attacks occurring after a multi-location attack. Fourteen (56 %) multi-location attacks were followed by another multi-location attack, suggesting that multi-location attacks are often followed by another multi-location attack.

Table 2 Anatomical locations of swelling in 33 HAE patients that had a multi-location attack as their first attack during the study period

Total attacks (<i>n</i>)	119
Attack at single location (<i>n</i>)	86 (72 %)
Attack at multiple locations (<i>n</i>)	33 (28 % of all attacks)
• Two locations	• 20 (60 % of multi-location attacks)
• Three locations	• 8 (24 %)
• Four locations	• 3 (9 %)
• Five locations	• 2 (6 %)
Peripheral	30 (90 % of multi-location attacks)
• Hand/hands	• 19 (58 %)/ 6 (18 %)
• Foot/feet	• 12 (40 %)/ 7 (23 %)
• Knee(s)	• 3 (9 %)
• Back	• 1 (3 %)
• Elbow(s)	• 1 (3 %)
• Buttock	• 1 (3 %)
• Chest	• 1 (3 %)
• Breast	• 1 (3 %)
Abdominal	16 (48 %)
Oro-facial-pharyngeal-laryngeal	10 (30 %)
Genitourinary	6 (18 %)

Table 3 Frequency of multiple location attacks in 119 HAE patients

Attack included	Attacks (<i>n</i>)	Multi-location attacks <i>n</i> (%)
Attack #1	119	33 (27 %)
Attack #2	49	17 (35 %)
Attack #3	23	12 (52 %)
Attack #4	10	3 (30 %)
Attack #5	6	0 (0 %)
Attack #6	4	2 (50 %)
Attack #7	3	0
Attack #8–12	5 ^a	0
Total	219	67 (31 %)

^a One patient had 12 attacks that were included in the study

Table 4 Overview of the frequency of various courses of VAS scores in multi-location attacks

	<i>n</i> (%)	Examples in Fig. 1
Simultaneous increase or decrease of VAS scores at different locations with <20 mm difference in VAS score at any time point	10 (22 %)	A
Simultaneous increase or decrease of VAS scores at different locations with >20 mm difference in VAS score at >1 time point	16 (35%)	B
Increase of VAS score of one location decrease of VAS score of the other with >20 mm difference in VAS score	13 (28 %) ^a	C
Start of location 2 >30 min after location 1	5 (11 %)	D
End of location 2 >2 h after location 1	2 (4 %)	E

^a Two patients had three affected areas of which one location in each patient showed a different clinical course

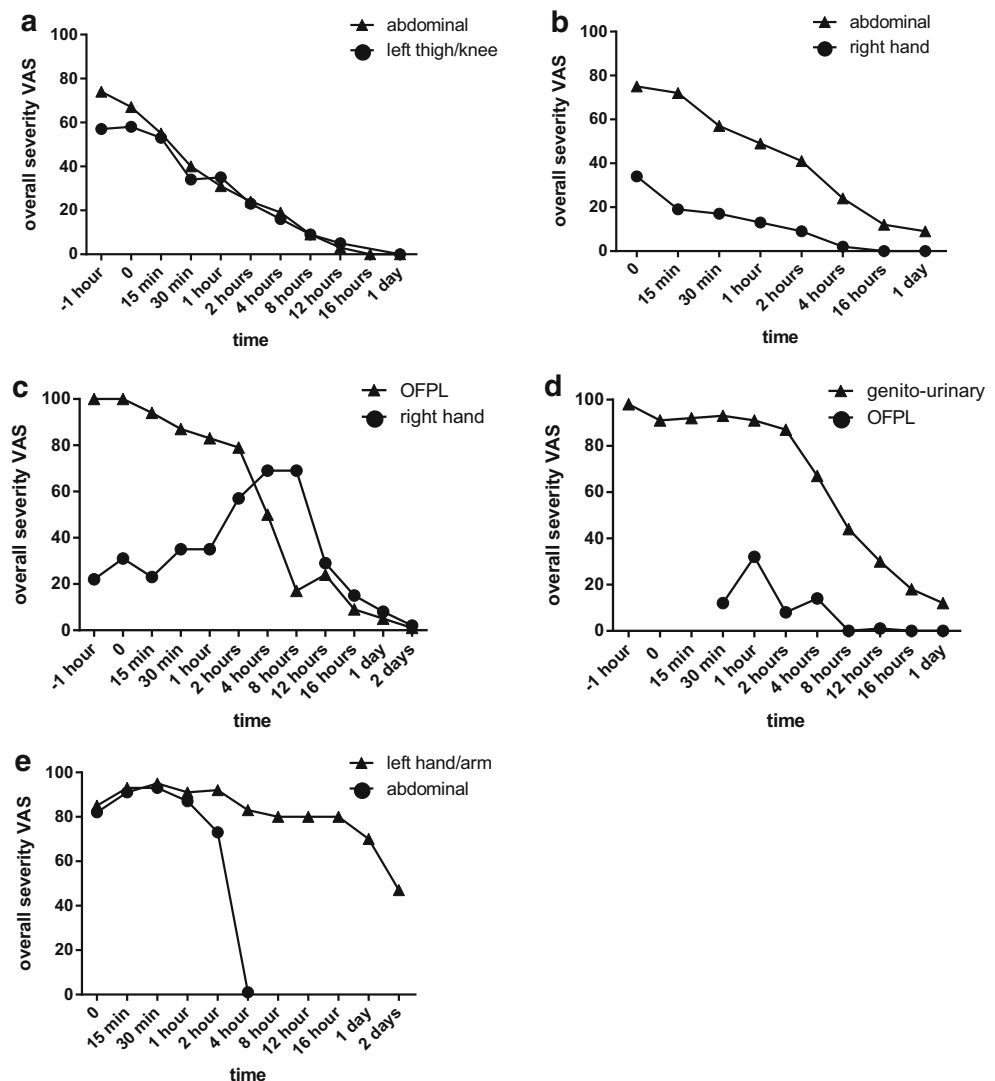
VAS Scores of Multi-location Angioedema Attacks

VAS scores for overall severity of symptoms were collected for each location separately, except for the cases in which a patient had two or more peripheral attack locations. In the latter case, only one overall severity VAS was filled in for the symptoms at various peripheral locations combined. Therefore, overall severity VAS data from two or more different locations were available for 46 attacks.

The course of the overall severity VAS scores for the different locations of multi-location attacks could be discriminated in five different patterns (Table 4; Fig. 1). As a first pattern, symptoms at different sites had a comparable course: they either increased or decreased together. This pattern was subdivided in cases in which VAS scores of the different locations at no point in time differed by more than 20 mm ($n=10$) and in the cases in which the difference in VAS scores at some time point was more than 20 mm ($n=16$). A third pattern showed an increase of VAS score in one location,

Fig. 1 Examples of the course of overall severity VAS scores at two locations. Data of five patients are depicted, the actual anatomical locations involved are given.

Example A: VAS scores in abdomen and left thigh and knee differ less than 20 mm and decrease simultaneously. Example B: VAS scores in abdomen and right hand differ by more than 20 mm until 16 h after onset but the course is similar. Example C: OFPL VAS scores start at 100 mm and rapidly drop after 2 h, while VAS scores of the right hand start at 20 mm and increase with almost 50 mm until 8 h after saline infusion. Example D: Initially, there are only genitourinary symptoms, and 1 h after drug infusion, VAS scores show a spike in OFPL symptoms. Example E: VAS scores of abdominal symptoms fully resolve between 2 and 4 h after drug infusion, while symptoms in the right arm last for 2 days



whereas the VAS score of the other location decreased on at least one time point ($n=13$), leading to a difference in VAS scores of >20 mm in the course of the attack. In a fourth category, the attack initially was a single location attack with a second location becoming manifest later ($n=5$). Finally, in a fifth category, symptoms at one location had resolved, while symptoms at another location were still at least moderate, i.e. >20 mm by VAS, two time points later ($n=2$).

Six patients that received saline treatment experienced a multi-location attack. In four of the saline-treated patients, VAS scores showed a similar course. In one saline-treated case, OFPL symptoms were slowly resolving, while symptoms in the right hand were still developing (see Fig. 1, example C). In another patient, abdominal symptoms started to resolve 15 min after start of saline infusion while symptoms in the right and left foot still worsened and did not decrease until 4 h after start of saline treatment.

Altogether, in 26 (56 %) patients, the VAS scores in all locations trended together. In 18 episodes (44 %), this was not the case.

Course of Single Versus Multi-location Attacks

In general, overall severity VAS scores did not differ between the most severe location of a multi-location attack and the overall severity VAS score of a single location attack. However, VAS scores of the most severe location of multi-location attacks were significantly higher 1 h before rhC1INH respectively saline infusion ($p=0.019$) and significantly lower 48 h after infusion ($p=0.0036$), compared to those of single location attacks.

The time until all symptoms had become minimal, i.e. were scored below 20 mm on VAS, was significantly longer in multi-location attacks (median, 480 min; interquartile range, 183–1107 for multi-location attacks) as compared to single location attacks (median, 241 min; interquartile range, 77–505 min; $p=0.015$).

CRP in Single Versus Multi-location Attacks

CRP levels of patients with a multi-location attack during the study period did not significantly differ from patients that did have single location attacks, except at 22 days after the attack when CRP levels in the multi-location group were higher ($p=0.013$). The lowest CRP levels were found in patients that only had one severe attack and only in a single location ($n=48$); at any time point, CRP levels in this group were lower than in patients that had more than one angioedema attack during the study period ($n=49$) (screening: $p=0.002$; at 45 min before treatment: $p=0.0004$; at 24 h after start of treatment: $p=0.013$ and at 22 days after the attack $p=0.0002$).

Discussion

The aim of this study was to evaluate the frequency and clinical symptoms of multi-location attacks in patients with HAE. Four main findings regarding such attacks were obtained. First, more than a third (40 %) of the HAE patients included had at least one multi-location attack during the study. Secondly, symptoms could occur in up to five anatomical locations in individual patients. Thirdly, symptoms in different locations seemed to wax and wane together in most attacks. And lastly, patients with a multi-location attack had a higher chance that their subsequent attack also was a multi-location attack as compared to patients with a single location attack.

Though multi-location attacks in HAE have been mentioned in the literature [1, 3–10], a detailed description of such attacks in a large cohort of patients has not been reported. Using clinical trial data does not have the recall bias of retrospective studies using patient questionnaires. Therefore, considering the number of attacks, the number of patients, as well as the methodology used, the results reported here give a reliable estimate of the occurrence of multi-location attacks in HAE. Since most attacks in this analysis were treated with rhC1INH, the course described for these attacks may not represent their natural history.

Our data support that attacks located at multiple anatomical sites are common in HAE, occurring in about 30 % of severe attacks. Previous studies reported that 25 up to 55 % of attacks at hospital admission were multi-location attacks [7–9]. Likewise, data from patient questionnaires showed that 24 % of HAE patients had a multi-location attack as their last attack [6] and 50 % of patients reported to have had a multi-location attack in the past [7]. The multi-location attacks reported in our study involved various combinations of distinct and sometimes remote anatomical sites. This observation was also made in a study with patients experiencing an abdominal attack; 51 % of patients also had swellings at other sites than the intestine [9]. Furthermore, in general, symptoms at different anatomical sites tended to develop and resolve more or less simultaneously rather than having an independent course such as resolving in one place while emerging in the other. In the few patients in whom a second symptomatic location developed later in the course of the attack, the course of the symptoms at this new location mostly resembled that of the symptoms at the initial location. Though we observed in some attacks that one location resolved more rapidly than the other (see example E, Fig. 1), this pattern was the exception. Therefore, our data support that the course of most symptoms of different anatomical locations in one patient is comparable during an HAE attack. Differences in the course of some symptoms may reflect local differences of fluid resorption rate by the involved tissues rather than basic differences in the biochemical processes leading to angioedema. The finding

that symptoms can trend together in a number of symptomatic sites was noted before in a secondary analysis of RCT data by Vernon and colleagues [10]. This observation was based on patient symptom reports. However, in this secondary analysis, the symptom that reports data about multi-location attacks was not further analysed or shown.

The finding that multi-location attacks tend to reoccur in some HAE patients has not been previously described to our knowledge. Additional investigations are necessary to confirm this since the subgroup with multi-location attacks and subsequent attacks in this study was relatively small. At the moment, we can only speculate about the reasons for this observation.

Angioedema attacks in HAE can apparently be triggered by local activation of factor XII due to insufficient control by C1INH by minor trauma [1]. An intriguing question is how symptoms can occur at multiple sites in the body during an attack which is triggered by a local activation process. One may postulate in particular cases that such local activation processes occur at two different places in the body. However, here, we report that the course in time of symptoms at various sites of multi-location attacks is quite comparable, which is unexpected in case angioedema at the involved sites would be triggered by independent local activation processes. Moreover, it is difficult to envision that multiple local activation processes would occur so frequently, i.e. in about 30 % of the severe attacks, and would occur at more than two places—i.e. at up to five places—in the body at the same time. Therefore, we postulate that the data reported here support the hypothesis that local angioedema formation in HAE patients result from a systemic rather than a local activation process. We suggest that this systemic activation process involves fluid-phase activation of factor XII and the contact system leading to increased levels of bradykinin and breakdown products in the circulation [14–18]. The bradykinin receptor B2 (B2R) is considered to be a key receptor increasing vasopermeability in HAE attacks [19, 20]. However, in case of a systemic activation of the contact system, the distribution of this receptor throughout the whole vasculature cannot explain localization of attacks. Therefore, we suggest reconsidering the role of the bradykinin receptor B2 (B1R). B1R can increase vascular leakage but, in contrast to B2R, is not constitutively expressed throughout the circulation. Involvement of B1R in angioedema formation in HAE has been suggested in a study in which increased vasopermeability in mesenteric microvessels in rats by active phase HAE plasma was shown to be dependent on both B1R and B2R [21]. We suggest that local up-regulation of B1R by cytokines such as interleukine-1 β and tumour necrosis factor- α (TNF- α) [22, 23] explains localization of angioedema triggered by a systemic activation of the contact system. Therefore, we suggest that local up-regulation of B1R at various anatomical sites possibly triggered by low systemic levels of such cytokines could explain the occurrence of multi-

location attacks in HAE. Notably, two recent analyses of CRP levels and cytokines in HAE patients support low grade systemic release of cytokines in many HAE patients [24, 25].

In conclusion, severe angioedema attacks often affect multiple sites in the body in HAE patients. These clinical observations support that HAE attacks are triggered by a systemic rather than a local activation process.

Authors and Contributors All authors participated in the study design and protocol for data analysis. The analyses were carried out by Zonne Hofman who also prepared the first draft of the manuscript. Erik Hack and Anurag Relan contributed to the interpretation of the data and revised the manuscript. All authors read and approved the final manuscript.

Conflict of Interest Zonne Hofman declares that she has no conflict of interest. Erik Hack has received consultancy fees from Pharming Technologies in the past. Anurag Relan is an employee of Pharming Technologies.

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