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Abstract: BACKGROUND: Hereditary angioedema with C1 inhibitor deficiency (C1-INH-HAE) is a rare inherited disease. In most HAE-affected subjects, defined trigger factors precede angioedema attacks. Mechanisms of how trigger factors stimulate the contact activation pathway with bradykinin generation are not well elucidated. In recent studies, hypersensitivity reactions and food were stated as relevant triggers. We investigated HAE affected people for possible hypersensitivity reactions or intolerances and their relation in triggering angioedema attacks. METHODS: A questionnaire was filled in, recording date of birth, gender, and self-reported angioedema attacks associated with the ingestion of foodstuffs, administration of drugs, hymenoptera stings and hypersensitivity reactions against inhalation allergens. All participants performed a skin prick test against inhalation allergens and food. In patients who stated an association of possible hypersensitivity with angioedema, a serological ImmunoCAP test was also performed. RESULTS: From the 27 women and 15 men analyzed, 79% stated trigger factors. From those food was mentioned in 36%. The suspected food included tomato, green salad, fish, citrus fruits, apple, onion, garlic, cheese, chili, kiwi, milk, tree nuts, strawberry, pineapple, shrimps, bread, banana, leek, chicken and alcohol, and were associated with abdominal angioedema. Neither the skin prick test nor the ImmunoCAP-test turned out positive for the tested food allergens. CONCLUSION: Food seems to be a relevant trigger factor, causing angioedema in HAE affected patients. The reason, however, is not IgE-mediated hypersensitivity, but most probably an intolerance reaction to food products.

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Food as a trigger for abdominal angioedema attacks in patients with hereditary angioedema

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Conclusion: Food seems to be a relevant trigger factor, causing angioedema in HAE affected patients. The reason, however, is not IgE-mediated hypersensitivity, but most probably an intolerance reaction to food products.

Keywords: Hereditary angioedema (HAE), Trigger factors, Allergy, Intolerance

Background

Hereditary angioedema with C1 inhibitor deficiency (C1-INH-HAE) is a rare inherited disease, due to mutations of the SERPING1 gene. Two different variants have been described. Type I is characterized by a quantitative decrease in C1-INH protein, in Type II, the C1-INH protein has a normal level, but is dysfunctional [1, 2]. C1-INH inhibits factors of the contact system including FXII and kallikrein, and controls the generation of vasoactive peptides such as bradykinin [3]. C1-INH-HAE is characterized by episodic attacks of subcutaneous and submucosal swelling affecting extremities, trunk, genitals, and face, and might be life threatening when upper airways and abdomen are affected [4, 5]. Although it is a systemic activation process, frequency and localization of angioedema are highly variable, depending on the trigger factors and the upregulation of bradykinin receptors 1 and 2 (B1R, B2R) on the endothelium [6, 7]. In 56 to 91% of HAE-affected subjects, defined factors or circumstances may trigger angioedema attacks [8, 9]. The most frequent trigger factors are emotions, mechanical trauma, infections, and, in women, hormonal causes, such as menstruation, pregnancy or intake of estrogen pills. In recent studies food ingestion has also been suggested to cause angioedema attacks in HAE [8–10]. Mechanisms of how food could trigger angioedema...
attacks have not yet been elucidated. Patients who are affected by angioedema induced by food, drugs or hymenoptera stings interpret the cause most often as an IgE-mediated hypersensitivity reaction. Recent studies have demonstrated an interaction of activated mast cells by an allergen and the contact activation pathway resulting in the production of bradykinin [11–13].

The aim of this study was to evaluate the influence of atopy or IgE-mediated hypersensitivity reactions to specific food, drugs or hymenoptera stings on angioedema attacks in HAE affected subjects. We assessed the prevalence of atopy in 42 HAE affected patients in correlation with the frequency of angioedema attacks and investigated trigger factors including food, drugs or hymenoptera venoms for specific IgE antibodies.

Methods
Patients
Patients from the Division of Haematology of the Cantonal Hospital Lucerne and from the Allergy Units of the University Hospitals of Berne and Zurich were included. They all fulfilled the diagnostic criteria for HAE [1]. All patients included are part of the Swiss HAE cohort study [9].

A questionnaire was sent to all participants: patients’ personal data, details of hypersensitivities/intolerances and symptoms (e.g., rhinoconjunctivitis, asthma, vomiting, stomach pain, diarrhea) were recorded. All participating patients gave their written informed consent. The protocol of this study received Ethics Committee approval from the Northwest - and Central Switzerland ethics committee. The study was conducted according to the principles of good clinical practice and adhered strictly to the ethical standards outlined in the Declaration of Helsinki [14].

Skin tests
Skin prick tests (SPT) with 7 commercially available aeroallergens (birch, ash, grass, mugwort, *Alternaria alternata*, house dust mite and cat dander) and 13 food antigen extracts (soy, hen’s egg, cow’s milk, celery, apple, codfish, shrimp, peanut, walnut, curry, chili, rye flour, and wheat flour) were tested (ALK-Abello, Hørsholm, Denmark). For banana and pine apple a prick-to-prick test was performed. If the wheal diameter was \( \geq 3 \) mm the test reaction was considered to be positive as recommended in the European standards for skin prick testing [15].

For the SPT with medications the drug powder dissolved in 0.9% saline was applied onto the skin of the forearms. If a wheel of at least 5 mm in diameter with surrounding erythema after 20 min was evident, the test was found positive [16].

Serologic tests
Serum samples were tested with the multitest Phadiatop Sx1 (timothy grass, birch, cultivated rye, mugwort, dog dander, cat dander, *Cladosporium herbarum, D. pteronyssinus*) and the multitest Fx5 (egg white, cow’s milk, fish (cod), wheat flour, peanut, soy bean). Specific IgE (sIgE) and total IgE were determined by ImmunoCAP FEIA (Thermo Fisher Scientific/Phadia, Uppsala, Sweden) according to the manufacturer’s directions for use. sIgE levels > 0.35 kUA/L (RAST class \( \geq 1 \)) were considered positive. In one patient IgA and anti-transglutaminase IgA was performed (Thermo Fisher Scientific/Phadia, Uppsala, Sweden).

Data handling
Clinical information was collected in each study center and transmitted to the administration site of the responsible researcher. Data were entered into the electronic database. If data were incomplete, the participant was contacted for specific clarification. The final dataset was pseudonymised and prepared for analysis. The pseudonymisation key is stored at the administration site.

For evaluating attack frequency we considered the results from the Swiss HAE cohort study [9] and assumed that sensitization patterns and attack frequency at the time point of the 2012-evaluation were stable.

Results
The analysis was based on 42 consenting patients (27 women and 15 men) with a mean age of 45 years (SD 16.1), all completed the questionnaire, conducted a skin test and consented to provide blood samples.

Trigger factors
Trigger factors causing HAE were indicated by 79% (23 women, 10 men). The most frequent trigger was emotion with 79.7% (18 women, 8 men) followed by trauma with 55% (12 women, 6 men) food 36% (10 women, 2 men), drugs 6% and hymenoptera stings 6% with 2 women each. Patient characteristics and trigger factors are presented in Table 1.

Atopy in HAE affected patients
Atopy documented by positive skin prick tests was identified in 29% (9 women, 3 men). Grass and tree pollen were the most prevalent allergen sources, followed by house dust mites, cat dander and mugwort. Ten of the 12 sensitized subjects were symptomatic with rhinoconjunctivitis (Table 1).

Association of self-reported hypersensitivity- or intolerance reaction and angioedema
Trigger factors were interpreted by the subjects themselves in 57% (11 women, 2 men), as an IgE-mediated hypersensitivity reaction. Four of these 13 subjects were
indeed confirmed to be atopic (Tables 1 and 2). In all the twelve subjects with food as a trigger, abdominal angioedema was induced. The included food were tomato (1), green salad (1), fish (2), citrus fruits (2), apple (3), onion (3), garlic (3), cheese (2), chili (2), kiwi (1), milk (3), tree nut (1), peanut (1), strawberry (2), pineapple (3), shrimps (1), bread (1), banana (1), leek (1), chicken (1), chamomile (1) and alcohol (1). However skin prick test for the specific food was negative in all 12 participants and none of the 11/12 tested patients with multitest fx5 and single food proteins had specific IgE (Table 2). Two women each mentioned bee/wasp venom, and drugs as a trigger. No specific IgE to the recombinant venom allergens of Api m1, Api m10 or Vesv5 were detected. In the two subjects with assumed drug induced angioedema, SPT of acetylsalicylic acid (ASS) in one and ASS combinations Pretuval®, NeoCitran® and the antidepressant Deroxat® (paroxetine) in the other patient resulted negative. Drug intake was not concomitant with reactions to hymenoptera venoms (Table 2). Four subjects complained of urticarial episodes. One atopic patient suffered from acute urticaria, 3 non atopic patients suffered from acute, inducible (physical) and aspirin induced urticaria (AIU) each. The one with AIU mentioned an association with urticaria and HAE typical angioedema. The other three did not observe an association between their urticaria and angioedema.

Frequency of angioedema in atopic and non-atopic subjects
There was no difference in the incidence of HAE attacks in atopic and non-atopic subjects (Table 3).

Discussion
We investigated 42 participants (31%) of the Swiss HAE cohort for suspected self-reported hypersensitivity or intolerance reactions as trigger factors for their angioedema attacks [9]. The majority of the participating individuals (79%) stated that trigger factors preceded angioedema attacks. Emotions, followed by trauma, were mentioned most frequently, which is in line with the current literature [8, 9]. Hypersensitivities or intolerances to food, medications or hymenoptera stings were stated by almost half of the patients with trigger factors (Table 1).

IgE-mediated hypersensitivity with mast cell activation can be associated with heparin release and a consequent bradykinin generation [11–13, 17, 18]. Almost one third of our cohort was atopic. This proportion reflects the general population’s prevalence of atopy in Northern Europe and in industrialized countries [19–21]. In our cohort no difference of attack frequency was documented between atopic and non atopic subjects. With regard to the question of whether suspected hypersensitivity or intolerance is associated with angioedema, there was no relevant difference between atopic (33%) compared to non-atopic subjects (30%). Based on our data, atopy does not predispose HAE affected subjects to suffer from more frequent angioedema attacks (Table 3).

Interestingly in all 12 subjects the specific food which was mentioned as a trigger factor seemed to induce abdominal angioedema attacks (Table 2). However, in none of them specific IgE against the indicated food products could be documented, neither by SPT nor by serological tests. Therefore, food induced abdominal angioedema attacks in these subjects are triggered most probably by an intolerance reaction due to unknown mechanisms. Most of the food mentioned by the investigated subjects such as cheese, alcoholic beverages, fish, tomatoes, strawberries, pineapples, nuts, citrus fruits and kiwis contain or release histamine [22]. Therefore a histamine intolerance reaction is probably associated with the induction of angioedema. However, a clear allocation of food inducing histamine intolerance remains difficult and a reliable laboratory test for objective diagnosis is lacking [23–25]. Three patients suffered from a known lactose intolerance and they stated a clear

### Table 1 Characteristics of 42 patients

| Parameter                                      | Number (men/women) |
|------------------------------------------------|--------------------|
| Patients                                       | 42 (15/27)         |
| mean age (years)                               | 45 (SD 16.1)       |
| HAE variants                                   |                    |
| Type I                                         | 41 (0/41)          |
| Type II                                        | 1 (1/0)            |
| Trigger factors                                |                    |
| Emotions                                       | 26 (8/18)          |
| Trauma / Mechanical trigger                    | 18 (6/12)          |
| Hormones<sup>a</sup>                           | 17 (0/17)          |
| Infection                                      | 13 (3/10)          |
| Food                                           | 12 (2/10)          |
| Drugs                                          | 2 (0/2)            |
| Bee/Wasp sting                                 | 2 (0/2)            |
| Total                                          | 33 (10/23)         |
| Atopy                                          |                    |
| Patients                                       | 12 (3/9)           |
| Grass pollen                                   | 10 (1/9)           |
| Tree pollen                                    | 10 (3/7)           |
| House dust mite                                | 5 (2/3)            |
| Cat dander                                     | 3 (1/2)            |
| Mugwort                                        | 3 (1/2)            |
| Self reported hypersensitivities/intolerances inducing angioedema |                |
| Atopic                                         | 4 (0/4)            |
| Non atopic                                     | 9 (2/7)            |

<sup>a</sup>menstruation, pregnancy or intake of estrogen pills
Table 2: Self reported hypersensitivity- and intolerance reactions associated with angioedema (AE) in atopic and non atopic subjects

| Patients                      | Self reported hypersensitivity/intolerance | SPT | Phadiatop Sx1, fS5; sIgE (CAP class 1–6) | Localisation of AE | AE induced by |
|-------------------------------|-------------------------------------------|-----|------------------------------------------|-------------------|--------------|
| Atopic, associated with AE (n=4) |                                           |     |                                          |                   |              |
| Female trees, grass, hdm, cat | tomato, green salad                        | positive for: grass, ash, cat | all negative | negative for: fS5, tomato, (4) | abdomen, food |
| Female trees, grass           | fish, citrus fruits                        | positive for: grass, birch | all negative | negative for: fS5 | abdomen, food |
| Female hdm                    | apple, onion, garlic, cheese, chili        | positive for: hdm | all negative | negative for: rApim1/10, Ves v5 | abdomen, food |
| Female trees, grass, hdm, cat | kiwi, onion, chili, fondue                 | positive for: birch, ash, grass, hdm | all negative | negative for: fS5, onion, apple, chili | abdomen, food |
| Non atopic associated with AE (n=9) |                                           |     |                                          |                   |              |
| Female yes, ns                | strawberry, chamomile, pineapple           | negative | negative | Sx1 negative | negative for: fS5, chamomile, strawberry, pineapple |
| Female garlic, shrimps, milk  | negative | negative | Sx1 negative | negative for: fS5, shrimps, garlic | abdomen, food |
| Female grass                  | milk, bread                               | negative | negative | Sx1 negative | abdomen, food |
| Female cheese, apple, banana, garlic, onion, leek | negative | negative | nd | nd | abdomen, food |
| Female grass, trees, hdm      | walnut, pineapple, chicken, ASS            | negative | negative for food allergens | Sx1 negative | negative for: fS5, ASS: mouth, eyelid food: abdomen |

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### Table 2 Self-reported hypersensitivity- and intolerance reactions associated with angioedema (AE) in atopic and non-atopic subjects (Continued)

| Patients | Self-reported hypersensitivity/intolerance | SPT | Phadiatop Sx1, fx5; sIgE; (CAP class 1–6) | Localisation of AE | AE induced by |
|----------|-------------------------------------------|-----|------------------------------------------|-------------------|-------------|
|          | Inhalation allergens                       | Food | Drug | Bee--Wasp-stings | Aeroallergens | Food | Allergens | Bee--Wasp | allergens |
| Female   | yes, ns                                   | pineapple, peanut, apple, orange, strawberry | negative | negative | Sx1 negative | negative | for: fx5, apple, strawberry, orange, pine apple | nd          |
| Male     | alcohol, milk                             | negative | negative | Sx1 negative | fx5 negative | nd      | alcohol: extremities, abdomen, food |
| Male     | fish                                      | negative | negative | Sx1 negative | fx5 negative | nd      | abdomen, food |
| Female   | Paroxetine®, Pretuval®, Neo-citran®       | negative | negative for Paroxetine®, Pretuval®, Neo-citran® | Sx1 negative | nd      | nd      | face, abdomen, drugs |

**AE** angioedema, **SPT** skin prick test, **hdm** house dust mites, **ASS** acetylsalicylic acid, **ns** not specified, **nd** not done

*SPT: 7 Aeroallergens: birch, ash, grass, mugwort, Alternaria alternata, house dust mite and cat dander
*SPT 14 food allergen extracts: soy, hen’s egg, cow’s milk, celery, apple, codfish, shrimp, peanut, walnut, pepper, curry, rye flour, and wheat flour (aeroallergen extract and food allergen extract by ALK-Abelló, Hørsholm, Denmark). Only positive results mentioned

Multitest Sx1: Specific IgE for: timothy grass, birch, cultivated rye, mugwort, dog dander, cat dander, Cladosporium herbarum, D. pteronyssinus

Multitest fx5: Specific IgE for: egg white, cow’s milk, fish (cod), wheat flour, peanut, soy bean

( ) CAP class 1–4 of allergen specific IgE in kU/l: 0: < 0.35; 1: 0.35–0.7; 2: 0.71–3.5; 3: 3.51–17.5; 4: 17.5–50

Anti tg IgA-Ab: anti transglutaminase IgA antibodies (marker for celiac disease)
association between HAE attacks and intake of cow’s milk products. In lactose intolerance the unabsorbed lactose leads to osmotic diarrhea and gas production causing flatulence and abdominal pain. In these subjects also a heightened activity of the innate mucosal immune system with increased counts of mast cells and lymphocytes is described [26, 27]. Which of these mechanisms are influencing the formation of angioedema in HAE remains to be analyzed further. For one subject, who declared bread as a cause of angioedema celiac disease was excluded with a negative test for anti-tissue transglutaminase IgA-antibodies.

This study corroborates that food is a relevant trigger factor for abdominal angioedema attacks in HAE affected subjects. However the underlying pathomechanisms for activation of the contact activation pathway with bradykinin formation in the investigated subjects seem to be intolerance reactions rather than IgE-mediated hypersensitivity. In these patients a careful individual nutritional counseling is recommended with the aim of a targeted avoidance of the food concerned.

Little data are available on urticaria in HAE [28, 29]. The prevalence of urticaria in our cohort was 10%. This proportion was lower compared to the general population or a recently described survey of a HAE cohort, which is most probably explained by the small number of our investigated population [28, 30].

An association of urticaria with typical HAE was only corroborated by the patient with AIU. Acute and physical urticaria did not seem to provoke HAE. These findings are emphasizing that mechanisms in AIU are different compared to acute or physical urticaria. In AIU most probably activated mast cells are involved but the exact pathomechanism is still not clear [31]. The drugs ASS, ASS combinations and Paroxetine provoked peripheral, facial and abdominal angioedema. According to the negative skin test results, non IgE-mediated hypersensitivity reaction (e.g pseudoallergy) most probably induced the symptoms [32, 33]. Further investigations are required to analyze the threshold of mast cell activation in the different subtypes of urticaria and pseudoallergy with a subsequent potential to induce the contact activation pathway with bradykinin release.

Two patients who stated a local reaction and an abdominal angioedema attack induced by hymenoptera stings, showed no sensitization to the major allergens rApi m1/10 and rVes v5 involved. In these patients, it was not allergy, but rather the pain of the sting and the stress that triggered the angioedema attacks.

Severe IgE-mediated hypersensitivity reactions most probably can induce bradykinergic angioedema attacks by induction of the contact activation pathway [12, 13]. Therefore if HAE affected subjects indicate triggers such as food, hymenoptera stings or drugs, which have the potential to induce severe IgE-mediated hypersensitivity reaction, specific IgE antibodies must be excluded. However intolerance reactions seem to be more important triggers than IgE-mediated mechanisms.

Strength and limitations
To our knowledge this is the first study that addresses food as a trigger factor in patients with HAE. Although the selected cohort is small, we consider the results valid. Self-reporting of trigger factors and symptoms carry the risk of reporting bias. A downside of this study is that no provocations tests with the incriminated food, suspected drug or a challenge sting test with a living hymenoptera has been performed.

Conclusion
Food products can be important trigger factors for abdominal angioedema attacks in HAE. The underlying pathomechanism most often is compatible with an intolerance reaction. IgE-mediated hypersensitivity reactions seem rarely cause angioedema in HAE. Studying trigger factors in HAE is essential to obtain a better understanding of the disease mechanisms.
Abbreviations
AIU: Aspirin induced urticaria; ASS: Acetylsalicylic acid; C1-INH: HAE: Hereditary angioedema with C1 inhibitor deficiency; sIgE: Specific IgE; SPT: Skin prick test

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Availability of data and materials
The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Authors’ contributions
US: carried out concept and design of the study, accumulation of data, analysis and interpretation of the data, performed writing/critical revision of the manuscript. LW: accumulation of data, critical revision of the manuscript. PS: accumulation of data, critical revision of the manuscript. AH: accumulation of data, analysis and interpretation of the data, writing/critical revision of the manuscript. LK: accumulation of data, critical revision of the manuscript. The authors read and approved the final manuscript.

Competition interests
The authors declare that they have no competing interests.

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