An investigation into the triggering factors of edematous attacks in hereditary angioedema

Ph.D. Thesis

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Budapest
2017

1. INTRODUCTION

1.1. Hereditary angioedema

Hereditary angioedema caused by C1-inhibitor (C1-INH-HAE) is a genetic disorder of autosomal dominant inheritance. The hallmark of this disorder is the recurrence of subcutaneous or submucosal edema-formation, which can lead to life-threatening complications.

C1-INH-HAE is a rare disease with an estimated population incidence of 1 per 10,000 to 1 per 50,000. The data of the Hungarian HAE Center show a domestic prevalence of 1.71%. More than 400 genetic mutations have been described to cause C1-INH deficiency, the abnormality underlying types I and II of C1-INH-HAE. This disorder is therefore characterized by genetic heterogeneity – and diverse phenotypes, – even in the case of the mutations that occur within the same family. The differences between geno- and phenotype suggests that some other, yet unknown factor(s) that might influence the manifestations of the disease in addition to hereditary determination.

Clinical symptoms

Two major categories of the clinical symptoms can be defined depending on the location of edema formation. Subcutaneous edema occurs on the face, the extremities, the trunk, and the genitals. Submucosal edema involves the mucosal lining of the upper airways, or of the gastrointestinal tract. In the case of the former, airway obstruction may cause rapid asphyxia. Gastrointestinal edema may mimic the symptoms of an ‘acute abdominal catastrophe’, including colicky abdominal pain, vomiting, and post-attack watery diarrhea.

Although the symptoms may occur at any age, the usual age at onset is 6 to 8 years. The edematous episode lasts for 24 to 72 hours; however, it may persist for as long as a week in more severe cases. The time of onset, frequency, duration, and severity of the symptoms vary within each patient, and great differences can be observed within the same family.

1.2. The exploration of triggering factors in edematous episodes of hereditary angioedema

The time of the onset of the individual attacks is generally unpredictable; however, the circumstances of occurrence and the patients' observations appear to implicate certain triggering factors. Elucidating the role of the latter could result in a better understanding of the etiology of the edematous episodes. The empirical observations by the patients and by the medical professionals responsible for their management have identified a number of events that carry a higher risk of the occurrence of a C1-INH-HAE attack. Such events include physical exertion, mechanical trauma, mental stress, infections, menstruation, pregnancy, oral contraceptive use, medical procedures, changes of the weather, and treatment with certain medicinal products.

1.3 The role of mental stress in the pathogenesis of edematous episodes

Because our earlier study identified mental stress as the most common inducer of edema-formation, we initiated a comprehensive research to investigate this possible triggering factor. Chronic stress, which is a generic risk factor for a range of disorders, may enhance the probability of contracting many diseases, or it might influence the course of pre-existing conditions.

1.4 The evaluation of urinary sediment parameters in patients with hereditary angioedema

Various infections may also play an important role in the occurrence of edematous attacks. Notwithstanding this, the effects of urinary tract infections (UTIs), which are among the most common infections, have not yet been studied. Subclinical colonization by urinary pathogens (with symptom-free bacteriuria) is similarly common. According to the current European guidelines, the treatment of symptom-free bacteriuria is necessary only if this has been shown to be beneficial for the patient.

1.5 The efficacy of short-term prophylaxis in the prevention of angioedema attacks

It has long been known that various medical interventions may trigger edema-formation and therefore, it is justified to administer adequate and appropriate short-term pre-treatment before the procedure. Surgical interventions (e.g. dental procedures, any kind of surgery), or diagnostic procedures (such as endoscopy of the stomach, rectum, larynx, or bronchi) may cause tissue trauma, and this explains their capability for inducing an edematous attack. Our studies evaluated the efficacy and safety of short-term prophylaxis administered before medical intervention. This we did by comparing the number of edematous episodes that had occurred before C1-INH-HAE was diagnosed with that observed after diagnosis. In other words, we determined the difference in the numbers of the attacks associated with medical interventions performed without/with short-term prophylaxis.

2. OBJECTIVES

2.1 Overall investigation of the role of triggering factors

Our objective was to perform systematic and comprehensive investigation of the triggering factors associated with hereditary angioedema. Accordingly, our study included a long follow-up period – to obtain longitudinal information, and a prospective study period focused on the evaluation of selected, most common triggering factors. Familiarity with the latter could result in a better understanding of the pathomechanism of C1-INH-HAE, and might allow individualized management and counseling.

2.2 Evaluation of the role of mental stress in triggering edematous attacks

Our investigations described in the preceding sections identified mental stress as one of the most common triggering factors. Therefore, we used a triple approach to study its role in inducing edematous attacks. First, we surveyed the level of the stress perceived by the patients, along with the coping ability of the latter. Next, we measured serum cortisol levels during edematous attacks, as well as in symptom-free periods. Finally, we studied glucocorticoid receptor polymorphisms, which also influence the stress response.

The glucocorticoid receptor (GR) is a member of the nuclear receptor family. Many studies suggested a relationship between GR polymorphisms and various diseases. The presence of the polymorphous allele can lead to an altered glucocorticoid sensitivity and thereby influence the occurrence, or the course of disorders. Although several GR polymorphisms have been

identified, only a couple of these have clinical or functional significance. We studied three different single nucleotide polymorphisms (SNPs – namely BClI, N363S, and 9β) of the GR gene.

2.3 Evaluation of the role of UTIs in triggering edematous attacks

Previously, we conducted comprehensive studies into the attack-inducing capability of infection by *Helicobacter pylori*. This infection has been shown to increase the number of edematous episodes remarkably. By analogy to this relationship, we planned to study the role of UTIs in inducing edematous episodes in hereditary angioedema. In the first, retrospective stage of our study, we examined whether the presence of an UTI is associated with a greater frequency of HAE attacks.

2.4 The efficacy of short-term prophylaxis in the prevention of angioedema attacks

The most familiar triggering factors are the medical procedures performed with diagnostic or therapeutic intent. It has long been observed that these are most likely to entail an edematous episode and thus, their prevention is indispensable. Nevertheless, only a few relevant studies have been performed, focusing on dental procedures and case reports. Our objective was to analyze the efficacy and safety of short-term prophylaxis administered before medical interventions.

3. PATIENTS AND METHODS

3.1. The investigation of triggering factors in edematous episodes of hereditary angioedema

In the first, retrospective phase of our study, we reviewed the records made by 92 C1-INH-HAE subjects in their patient diaries, according to a standardized protocol. The diagnosis of C1-INH-HAE had been verified by genetic and complement testing. We used statistical methods to analyze the distribution of the 3176 edematous episodes recorded by these patients over the initial 7 years. Twenty-seven of these patients participated in the second stage of the study. They were asked to keep record of possible triggering factors every day, regardless of whether or not an attack has occurred. The 27 patients kept daily records over 7 months, identified 652 possible triggering factors, and recorded 243 edematous attacks.

3.2 The role of mental stress in edematous episodes

We genotyped 139 C1-INH-HAE patients; 160 healthy Hungarian individuals served as controls for comparing the SNPs occurring in the glucocorticoid gene. The complete genomic DNA was extracted from peripheral blood, using an appropriate DNA isolation kit. BclI and N363S polymorphisms were detected with allele-specific polymerase chain reaction (PCR), whereas the A3669G polymorphism was identified with TaqMan SNP assay and real-time PCR. For each polymorphism, we sought relationship between their presence and the indices of disease severity. Moreover, we also investigated other metabolic properties possibly related to carrier status according to the literature.

We collected blood also for cortisol and complement determinations. Samples obtained during edematous episodes, or in symptom-free periods between the attacks were available. Total cortisol level in the plasma was measured with an electrochemiluminescence immunometric assay. An immunoenzymatic assay kit was applied to determine functional C1-inhibitor levels.

3.3 The evaluation of urinary sediment parameters in patients with hereditary angioedema

The medical history and urinary sediment parameters of 139 symptom-free C1-INH-HAE patients were analyzed retrospectively. In total, the laboratory data of 1288 samples of urinary sediment samples (collected at annual follow-up visits) were available for analysis using various statistical methods.

3.4 Short-term pre-procedural prophylaxis in hereditary angioedema

Data from 137 C1-INH-HAE patients were reviewed. The duration of follow-up varied between 6 months and 30 years (median: 11 years).

We conducted a retrospective analysis, using a questionnaire compiled on purpose, and initiated a prospective study when the diagnosis of C1-INH-HAE was established. At the time of diagnosis, we informed the patients that the above-described medical procedures might trigger edematous attacks, and recommended introducing short-term pre-procedural prophylaxis following consultation.

4. RESULTS

4.1 The investigation of triggering factors in edematous episodes of hereditary angioedema

4.1.1 The initial phase of the study

Of the 140 patients with C1-INH-HAE established by genetic testing and complement studies, six remained symptom-free until the drafting of this thesis. In other words, 134 of them have had at least one edematous episode during their lives. The records in the patient diary were suitable for evaluation in 92 patients: 93% experienced subcutaneous, 80% abdominal, and 60% upper airway edema at least once in a lifetime. Eight of these 92 patients could not identify any triggering factor, whereas the remaining 84 suspected an underlying provoking factor at least on one occasion.

The 92 patients, who had maintained their diaries regularly, recorded more than 3000 attacks over the 7 years – that is, each patient experienced 4 to 5 episodes per year. The female patients reported, on average 4, whereas males identified 2.7 different triggering factors. Altogether 2187 (68.9%) subcutaneous and 1151 (36.2%) submucosal episodes occurred over 7 years. In 161 instances, edema-formation occurred both in the subcutis and in the submucosa (mixed location). Of the 1151 episodes of submucosal edema formation, 937 (29.5%) were abdominal attacks, and 214 (6.7%) involved the upper airways.

<u>The incidence of triggering factors by the total number of attacks</u>

According to the analysis of individual attacks, the patients suspected a

possible triggering factor in 30% of the 3176 episodes, i.e. in nearly 1000 instances. The etiology could be identified in 23.64% of subcutaneous, 38.31% of abdominal, and 28.50% of upper airway attacks. In these, major triggering factors were emotional stress (21%), physical exertion (17%), and changes of the weather (15%).

The distribution of triggering factors by the location of edema formation

We grouped the attacks into the categories of subcutaneous and submucosal episodes. Then divided the latter into the subsets of abdominal or upper airway episodes, and analyzed those with a known triggering factor. As shown by the results, the triggering factors differed by the location of edema formation. Subcutaneous edema was most often induced by physical exertion (24%), followed by trauma (17%), and stress (15%). In the case of abdominal attacks, stress was the most common triggering factor (27%), followed by menstruation (17%), and changes of the weather (15%). In upper airway edema, infections and menstruation were the leading causes (26-26%), followed by stress (22%). The differences between these distributions are statistically significant ($p<0.0001$).

4.1.2 The second phase of the study

Twenty-seven patients participated in the second stage of our study. They were asked to keep record of possible triggering factors every day, regardless of whether or not an event carrying the risk of inducing an edematous episode of C1-INH-HAE has occurred. These 27 patients recorded 365 attacks and 882 possible triggering factors over 7 months. Of the 365 episodes, the patients could identify a possible triggering factor in 246. These numbers reflect the

reversal of the ratios of the episodes with/without a triggering factor, as the etiology was known in 67%, and unclear in only 26% of the attacks. The distribution by location of the 365 episodes with known etiology was as follows: 234 were subcutaneous, 114 abdominal, and 17 upper airway attacks.

The probability of an episode by individual triggering factors

The individual triggering factors were involved in the following proportions of edematous attacks: menstruation – 63% (n=38/60), infection 38% (n=28/74), stress 26% (n=53/199), physical exertion 25% (n=41/167), changes of the weather 21% (n=58/274) and exhaustion 17% (n=16/92).

4.2 The role of mental stress in edematous episodes

4.2.1 Hormone levels

There was a significant difference between total serum cortisol levels measured in blood samples taken during edematous episodes, or in attack-free periods (paired Wilcoxon test, p=0.004). In particular, mean total serum cortisol level was 9.679 ± 4.68 µg/dL during attack-free periods and 14.89 ± 11.58 µg/dL during attacks.

4.2.2. Genotyping

The allele frequencies of the N363S, BclI, and A3669G polymorphisms were not different between C1-INH-HAE patients and the controls. However, homozygous A3669G carrier state was significantly less common (p=0.037, statistical power: 59%) among C1-INH-HAE patients than in the control population.

The relationship between the A3669G carrier state and cortisol levels in patients with C1-INH-HAE

During attack-free periods, serum cortisol levels were significantly ($p=0.0173$) lower in carriers of the A3669G polymorphism. The same was found in blood samples obtained during edematous episodes; however, this difference was not statistically significant ($p=0.0653$).

In carriers of the polymorphism, cortisol levels were significantly lower even after the exclusion of the episodes rated 'severe' by the patients ($p=0.0148$), or of those involving the upper airways ($p=0.0204$). It should be noted that the attacks of these types are potent stressors and as such, can mask the effect of the polymorphism.

The analysis of metabolic parameters (BMI, presence of hypertension or of diabetes) revealed higher BMI in carriers of the 9β polymorphism, as well as the proportion of hypertensive patients was significantly greater among homozygous carriers of the BclI polymorphism.

4.3 The evaluation of urinary sediment parameters in patients with hereditary angioedema

4.3.1 The correlation of bacteriuria and total number of attacks

First, we analyzed the findings of the 1288 urinary sediment analyses and related attack numbers. Bacteria were identified in 298 of these samples. Although the diverse numbers of urine samples available per patient introduces statistical bias, we did find a positive correlation between bacteriuria and the number of attacks per year ($p<0.0001$).

In order to avoid the 'statistical trap' mentioned above, we analyzed three randomly selected samples per patients. Then, we repeated the analysis in all three groups. We concluded that edematous attacks occur in significantly greater numbers in the presence than in the absence of bacteriuria.

Having performed the analyses outlined above, we compared the number of attacks occurring over a year with the number of urine samples positive or negative for bacteriuria. Seventy-six of our patients had both positive and negative samples and within this subset, the number of edematous episodes was significantly ($p<0.0001$) greater if the corresponding urine sample was positive for bacteria.

4.4 Short-term pre-procedural prophylaxis in hereditary angioedema

4.4.1 Surgical and diagnostic procedures followed by an edematous episode – before the diagnosis of C1-INH-HAE

According to the review of the medical records and of the questionnaires completed by the patients, 202 (113 dental ad 89 diagnostic/surgical) procedures were performed before C1-INH-HAE was diagnosed. Seventy-four out of 126 patients (58.7%) reported 100 dental procedures and 39 diagnostic/surgical interventions, which were followed by an edematous episode within 48 hours. Edema formation occurred in the subcutis in 108/139, and in the airway mucosa in 31/139 instances.

Fifty-seven patients underwent non-dental intervention on 89 occasions (mostly tonsillectomy, adenotomy, and appendectomy). Thirty-nine of these

89 medical interventions led to an edematous episode; this corresponds to 43.8% of the procedures, and to 18.2% of the patients (n=23/126).

4.4.2 Surgical and diagnostic procedures with short-term prophylaxis – after the diagnosis of C1-INH-HAE

Fifty-seven of the 137 patients (42%) received short-term prophylaxis in 134 instances altogether. This involved administering danazol to 38, tranexamic acid to nine, and C1-INH concentrate to 87 patients. Of the 134 interventions performed under short-term prophylaxis, 13 were nevertheless followed by an edematous episode. In 10 of these 13 cases, edema formation occurred after a dental procedure, and following surgery in the remaining three. All ten patients had undergone prophylaxis earlier and had an uneventful postoperative/-procedural course subsequently. In this study, edema occurred despite short-term prophylaxis in 13% of patients (n=5/38) taking danazol, in 33% (n=3/9) of those receiving tranexamic acid, and in 6% (n=5/87) of subjects treated with C1-INH concentrate. Comparing the efficacy of the medicinal products used for short-term prophylaxis, we found that the administration of C1-INH concentrate significantly ($p=0.0096$) reduced the number of post-procedural attacks, compared with oral treatments (danazol and tranexamic acid). Of the 57 patients who had ever received prophylaxis, 23 (56%) experienced edema formation after medical interventions before their C1-INH-HAE was diagnosed.

The difference in the numbers of edematous episodes following surgery performed before or after establishing the diagnosis (39/89 vs. 3/55 with short-term prophylaxis) was statistically significant ($p<0.0001$).

5. CONCLUSIONS

1. Our study was the first in the world to undertake a systematic and comprehensive analysis of the role of various triggering factors in the occurrence of hereditary angioedema attacks. Ninety-one per cent of our patients could identify some circumstance or event, which might have contributed to the occurrence of an edematous episode. The most common triggering factors were physical exertion (71%), mental stress (59%), and mechanical trauma (59%). Considering all the edematous episodes together, the patients attributed one-third of these (i.e. approx 1000 attacks) to some triggering factor (most commonly mental stress). The attacks occurring in different locations had diverse triggering factors. Most often, patients, experiencing abdominal attacks were able to identify a triggering factor.

However, the events and circumstances suspected by the patients as triggering factors do not always induce angioedema. Of the triggering factors identified, menstruation was the most potent in increasing the susceptibility edema formation (in 68% of instances).

2. Based on our findings, the intensity of perceived stress was not significantly different among our patient groups. Coping ability, however, was different – that is, it was significantly superior in healthy subjects than in patients with angioedema or with C1-INH-HAE. Cortisol levels were significantly higher in blood samples obtained during edematous episodes than in those drawn in the periods between attacks – this is possibly related to the stress response. The incidence of various glucocorticoid receptor polymorphisms was similar in C1-INH-HAE patients and in the normal

population. We found lower basal cortisol levels in C1-INH-HAE patients who carry the 9β polymorphism.

3. The analysis of urinary sediment parameters revealed a relationship between the presence of bacteriuria and the clinical symptoms of hereditary angioedema. Patients with bacteriuria experienced significantly more edematous episodes during the one-year period before urinary sampling. The cumulative incidence of microhematuria among C1-INH-HAE patients exceeded the level suggested by previous literature data. We did not find a relationship between the presence of hematuria and danazol therapy. In our opinion, the treatment of asymptomatic bacteriuria may be justified in patients with C1-INH-HAE; however, this needs to be confirmed by further, prospective studies.

4. Medical interventions – and dental procedures in particular – increase the risk of edematous episodes. The efficacy of short-term prophylaxis with C1-INH concentrate was significantly superior to that of prophylactic treatment with danazol or tranexamic acid. In the majority of cases, a single dose of 500 IU C1-INH concentrate proved effective. Other authors suggested that treatment with a 1000-IU dose may further reduce the risk of edematous episodes and therefore, we need to consider administering the larger dose.

6. LIST OF ORIGINAL ARTICLES

6.1. Papers related to the Ph.D. thesis

Zotter Z, Csuka D, Szabó E, Czaller I, Nébenführer Z, Temesszentandrási G, Fust G, Varga L, Farkas H.
The influence of trigger factors on hereditary angioedema due to C1-inhibitor deficiency. *Orphanet J Rare Dis*. 2014; 9(1): 44. (IF=3.358)

Zotter Z, Nagy Z, Patócs A, Csuka D, Veszeli N, Kőhalmi KV, Farkas H.
Glucocorticoid receptor gene polymorphisms in hereditary angioedema with C1-inhibitor deficiency. *Orphanet J Rare Dis*. 2017; 12(1): 5. (IF=3.29*)

Zotter Z, Veszeli N, Kőhalmi KV, Varga L, Imreh É, Kovács G, Nallbani M, Farkas H.
Bacteriuria increases the risk of edematous attacks in hereditary angioedema with C1-inhibitor deficiency. *Allergy. 2016 Dec;71(12):1791-1793.* (IF=6.335*)

Farkas H, **Zotter Z,** Csuka D, Szabó E, Nébenfűhrer Z, Temesszentandrási G, Jakab L, Varga L, Harmat G, Karádi I. *(Co-First Authorship)*
Short-term prophylaxis in hereditary angioedema due to deficiency of the C1-inhibitor--a long-term survey.
Allergy. 2012; 64(12): 1586-93. (IF=5.883)

* The cumulative impact factor of the journal for the given year is not yet available.

The cumulative impact factor of the publications related to the thesis: 18.866

6.2. Other publications

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