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Research Article / Araştırma Makalesi

# Analysis of the Association of Allergic Disease in Pediatric Patients with Hereditary Angioedema

## *Herediter Anjioödemli Çocuk Hastalarda Alerjik Hastalık Birlikteliğinin Araştırılması*

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## Abstract

Hereditary angioedema (HAE) is a rare autosomal dominant disease that is derived from the deficiency or dysfunction of C1 esterase inhibitor (C1-INH). In studies about the diseases that can accompany hereditary angioedema, allergic diseases occur more frequently compared to the healthy population but no studies on this issue have been carried out. This study was conducted in order to determine the frequency of the comorbidity of atopic sensitivity and allergic diseases in patients with hereditary angioedema. 32 patients who were diagnosed with hereditary angioedema in the Paediatric Allergy Polyclinic of Mersin City Hospital between 2019 and 2021 were included in the study. In these patients, the information about the existence of atopic diseases was obtained from their files and recorded. While asthma was observed in 6 (18.8%), allergic rhinitis in 18 (46.9%), and urticaria in 2 (6.2%) patients, dermatitis was not observed in any of the patients. While Fx5 test was positive in 5 (15.6%) patients, inhalant allergen mix sps IgE was positive in 7 (25.9%) patients. The IgE value was above 100 in 12 (52.2%) patients, and the eosinophil level was above 4% in 16 (50%) patients. In conclusion, we speculate in this study that the association of atopic disease and atopic sensitivity is observed more frequently in patients with angioedema than in the healthy population. However, a study with a larger sample is necessary to confirm this finding.

**Keywords:** Hereditary angioedema, Allergy, Bradykinin

## Özet

Herediter anjiyoödem(HAE); C1 esteraz inhibitörün (C1-İNH) eksikliği veya disfonksiyonundan kaynaklanan; nadir görülen otozomal dominant bir hastalıktır. Herediter anjioödemle birlikte görülebilen hastalıklarla ilgili çalışmalarda alerjik hastalıkların sağlıklı popülasyona göre arttığı görülmüş, ancak şimdiye kadar bu konu ile ilgili bir çalışma yapılmamıştır. Bu çalışma herediter anjioödemli hastalarda atopik duyarlılık ve alerjik hastalıkların eşlik etme sıklığını belirlemek amacı ile yapıldı. Bu çalışmada 2019-2021 tarihleri arasında Mersin Şehir Hastanesi çocuk alerji polikliniğinde herediter anjioödem tanısı olan 32 hasta incelenmiştir. Bu gruptaki hastalarda atopik hastalıkların varlığı dosyalarından alınarak kaydedildi. Hastaların 6 (% 18,8)'sında astım, 18 (% 46,9)'inde rinit, 2 (% 6,2)'sinde ürtiker varlığı saptanırken, dermatit varlığına hastaların hiçbirinde rastlanılmadı. Fx5 testi hastalardan 5 (% 15,6)'inde pozitif iken, inhalan alerjen mix sps İgE 7 (% 25,9) hastada pozitif saptandı. IGE değerinin 12 (% 52,2) hastada 100 üstünde olduğu, eozinofil düzeyinin 16 (%50) hastada %4'ün üstünde olduğu gözlendi. Sonuç olarak bu çalışma ile herediter anjioödemli hastalarda atopik hastalık ve atopik duyarlılık birlikteliğinin sağlıklı popülasyona göre daha sık gözlendiğini düşünmekteyiz. Ancak doğrulamak için daha geniş hasta grubu ile çalışmalara ihtiyaç vardır.

**Anahtar Kelimeler:** Herediter anjioödem, Alerji, Bradikinin

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## 1. Introduction

Hereditary angioedema (HAE) is a rare disease that is derived from the deficiency or dysfunction of C1 esterase inhibitor (C1-INH) (1). The disease is observed equally in both sexes and is accepted to occur at a rate of approximately 1/50,000 (2). Three phenotypes of HAE have been determined up to now. C1-INH serum levels are low in type 1 HAE. In type 2 HAE, serum levels are normal or high but have insufficient functional activity. Although C1-INH levels are qualitatively and quantitatively normal in type 3 HAE, HAE clinical symptoms are observed. Angioedema begins before the age of 10 in half of the patients. Deterioration in the symptoms is seen during puberty in many patients (3). Angioedema attacks might affect any region of the body, but the most common and earliest finding is subcutaneous edema that develops on the faces, bodies, genital regions, and especially extremities of pediatric patients and is not accompanied by erythema and pruritus (4). Mechanical trauma is the most important factor inducing attacks in children (5, 6). The treatment of the disease falls into three main categories, acute attack treatment, short-term prophylactic treatment, and long-term prophylactic treatment. No treatment is recommended in attacks with mild edema since they usually regress spontaneously. However, acute attack treatment should be provided for patients if they have pharynx and larynx edema, cervical, lip, and face edema, severe body edema, or abdominal symptoms and severe extremities edema (7). Fresh frozen plasma and recombinant C1 esterase inhibitor icatibant treatments during the attacks are used to replace degraded C1 inhibitor in the treatment of the attacks. An important part of the treatment of HAE is the training the patient and family (8). In the studies that were conducted about the diseases that can accompany hereditary angioedema, allergic diseases occurred at increased frequency in patients with hereditary angioedema compared to the healthy population but no studies have been carried out on this issue. This study was conducted to determine the frequency of the comorbidities of atopic sensitivity and allergic diseases in patients with hereditary angioedema.

## 2. Materials and Methods

32 patients who were diagnosed with hereditary angioedema in the Paediatric Allergy Polyclinic of Mersin City Hospital between July 2019 and April 2021 were included in the study. The diagnosis of hereditary angioedema was made when low levels of C4 and C1 inhibitors together or lack of activity existed (5). In the patients in this group, information about the existence of accompanying asthma, allergic rhinitis, urticaria, and atopic dermatitis was obtained from their files and recorded. Asthma was defined via anamnesis (by querying about the existence of dyspnea and day and night coughing complaints) and respiratory functions (9). Allergic rhinitis was defined by performing food inhalant sps IgE, skin prick tests, and allergy tests in patients with complaints of sneezing attacks, frequent and watery nose flow, nasal congestion, and nasal itching (10). Atopic dermatitis was considered as a dermatosis that is chronic, itchy, and inflammatory (11). Urticaria was clinically evaluated as swellings in various parts of the body, in various shapes and sizes, pink-red, burning, stinging, and itching (12). Hemogram, eosinophil, total IgE, nutrient mix sps IgE (milk, egg, soy, wheat, nuts, fish), Phadiatop (inhalant allergen sps IgE), if applied, skin prick test results were obtained from the files and recorded. Skin prick test was performed epidermally with Dermatophagoides pteronyssinus (Dp), Dermatophagoides farinae (Df), meadow and grain pollen mix, weed pollen mix, tree pollen mix, olea pollen, alternaria, cockroach, cat and dog epithelium, milk, egg, wheat, soybean, peanut, hazelnut, beef, chicken, and fish mix (Alk) antigens. The tests were applied to the volar side of forearm, histamine hydrochloride (1 mg/ml) was used as a positive control and physiological saline solution was used as a negative control. The test result is evaluated 15 minutes later. For histamine reaction, a condition of >5 mm edema accompanied by erythema is required. An average induration diameter of ≥3 mm compared to the negative control in the skin test and accompanying erythema are considered positive.

Serum-specific IgE levels of the patients were studied with CLIA (Chemiluminescence Immuno Assay). Values of ≥0.35 kU/l were considered positive for food- and inhalant-specific IgE. Specific IgE levels of food allergens (egg, milk, fish, wheat, peanut, soybean) were evaluated with Fx5, and aeroallergen serum specific IgE levels were evaluated with Phadiatop. Eosinophilia was defined when the eosinophil level was above 4% in the complete blood count.

The approval of Toros University Clinical Research Ethics Committee was obtained for this study.

## 3. Results

There was a homogenous distribution in the study in terms of female and male patients. The mean age of the patients was 9.9±5.2 years.

Asthma was seen in 6 (18.8%) patients, rhinitis in 18 (46.9%) patients, and urticaria in 2 (6.2%) patients. However, dermatitis was not observed in any of the patients. In addition to positive Fx5 test in 5 (15.6%) patients, inhalant allergen mix sps IgE was positive in 7 (25.9%) patients. The IgE value was above 100 in 12 (52.2%) patients, and the rate of eosinophil level was above 4% in 16 (50%) patients.

The distribution of the inhalant allergen sensitivities detected was DP in 2 (22.2%) patients, grain pollen in 1 (11.1%) patient, grass pollen in 3 (33.4%) patients, olive pollen in 1 (11.1%) patient, and alternaria alternata in 2 (22.2%) patients (Table 1).

**Table 1.** Statistical results of patient data

| | **Frequency (n)** | **Percentage (%)** |
|---|---|---|
| **Gender** | | |
| Male | 16 | 50.0 |
| Female | 16 | 50.0 |
| **Existence of Asthma** | | |
| No | 26 | 81.3 |
| Yes | 6 | 18.8 |
| **Existence of Rhinitis** | | |
| No | 17 | 53.1 |
| Yes | 15 | 46.9 |
| **Existence of Urticaria** | | |
| No | 30 | 93.8 |
| Yes | 2 | 6.2 |
| **Existence of Dermatitis** | | |
| No | 32 | 100.0 |
| Yes | - | - |
| **Fx5** | | |
| Negative | 21 | 80.8 |
| Positive | 5 | 19.2 |
| **Inhalant allergen mix sps IgE** | | |
| Phadiatop Negative | 20 | 74.1 |
| Phadiatop Positive | 7 | 25.9 |
| **Total IgE level, IU/mL** | | |
| IgE<100 | 11 | 47.8 |
| IgE>100 | 12 | 52.2 |
| **Eosinophil** | | |
| <4% | 16 | 50.0 |
| >4% | 16 | 50.0 |
| **Allergen** | | |
| DP | 2 | 22.2 |
| Grain Pollen | 1 | 11.1 |
| Grass Pollen | 3 | 33.4 |
| Olive Pollen | 1 | 11.1 |
| Alternaria alternata | 2 | 22.2 |
| | **Mean±sd** | **Med (Min-Max)** |
| Age, Years | 9.9±5.2 | 9.5 (2-18) |

## 4. Discussion

This study was conducted in order to determine association of allergic diseases in pediatric patients with hereditary angioedema, a rare disease.

In the literature, there are no studies about allergic diseases in patients with hereditary angioedema. However, Nanda et al. (6) reported that asthma accompanied HAE in 5% of the patients and atopy in 15% of the patients in their study in which they evaluated the clinical characteristics of pediatric patients with hereditary angioedema (6). In the study by Björkman et al. in which they investigated comorbid diseases, there was two times more allergy, asthma, and atopic dermatitis in the patients (13). In our study, asthma accompanied HAE in 19% of the patients, allergic rhinitis in half of the patients, and recurrent urticaria in 6% of the patients. The incidence of asthma in our country was determined as 2.06% (14). Kurt et al. conducted the PARFAIT study with the age group of 6–15 years in 14 cities from different regions of Turkey and found that the incidence of allergic rhinitis was 22.7% in 6–7 age group in rural areas and 17.8% in the city centers (15). When all these results are considered together, it is concluded that both atopic diseases and atopic sensitivity are seen frequently in the patients with hereditary angioedema.

Deficiency of C1esterase inhibitor, which is the main mediator of the contact system, is seen in hereditary angioedema. The deficiency of C1 esterase inhibitor induces the activation of Factor 12 and causes subsequent increases in kallikrein and bradykinin. It was shown that the activation of the B2 receptor by the mediation of bradykinin plays an important role in the development of angioedema, which is associated with C1 inhibitor deficiency. High levels of bradykinin were detected in the plasma of patients with hereditary angioedema (16). Bradykinin is a strong vasodilator and proinflammatory peptide that causes fluid accumulation in the interstitium (17). Bradykinin also contributes to the pathogenesis of allergic inflammation and allergic cases (18, 19). It mediates the inflammation in patients with asthma owing to its bronchoconstrictor characteristics (18). Bradykinin, which is believed to be a strong mediator playing a role in allergic rhinitis as well, increased with the allergen provocation. It was also revealed that bradykinin receptor antagonists inhibit nasal allergic symptoms (19, 20). This information shows that allergic diseases might be increased in this population due to the rise of bradykinin in hereditary angioedema.

Although the pathogenesis of angioedema in hereditary angioedema is explained by the increase in bradykinin, the pathogenesis of this disease has not been fully clarified. If the pathogenesis is completely understood, the reason why allergic diseases are more common can be explained. However, further studies are necessary to confirm these assumptions.

The most important limitation of our study is having been conducted in a single center.

As a conclusion, we believe that atopic disease and atopic sensitivity are more frequently seen in patients with hereditary angioedema based upon the results of this study. However, a study with a larger sample size is necessary to confirm this finding.

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**Ethics**

**Ethics Committee Approval:** This study was approved by the Ethics Committee of the Toros University (Decision no: 50, Date: 15.04.2021).

**Informed Consent:** The authors declared that it was not considered necessary to get consent from the patients because the study was a retrospective data analysis.

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