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The attack localizations in C1 inhibitor deficient hereditary angioedema patients

C1 inhibitör eksikliği olan herediter anjioödem hastalarında atak lokalizasyonları

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Abstract

Background Hereditary angioedema (HAE) is a rare autosomal dominant inherited disease characterized by recurrent angioedema episodes and classified as HAE with C1-inhibitor (C1INH) deficiency (HAE-C1INH) and HAE with normal C1-inhibitor (HAE-nlC1INH). It may involve the face, larynx, upper airways, trunk, gastrointestinal system, genital area, and extremities. The angioedema attacks are disabling, and laryngeal edema can lead to asphyxiation and death if it is not treated successfully. We aim to investigate the association between the attack localizations and complement parameters of HAE C1INH patients.

Methods Patients with HAE-C1INH from Ege University Faculty of Medicine were included. Patients with HAE-nl-C1INH were excluded from the study. Data on the clinical records were obtained retrospectively. Sociodemographic data, age at disease onset, annual attack frequencies, attack localizations, and complement parameters were recorded.

Results One-hundred patients were in the study group. Fifty four percent of them were female. The majority of patients were HAE-C1INH type I (87%). The mean age at disease onset was 12.01 ±7.04 years. Plasma C4 levels were normal in eight patients (8.16%). The most frequently involved localizations were extremities (91%), gastrointestinal system (89%), and genital area (85%). Having a facial attack and erythema marginatum were both found to be correlated with the occurrence of laryngeal edema. Laryngeal edema was seen in 83.8% of the patients with erythema marginatum (P=0.010), and 75.9% of the patients with facial attacks (P<0.001).

Conclusion The correlation between erythema marginatum and laryngeal edema was not reported in previous studies. Due to the unpredictable and fatal nature of the laryngeal attacks, all HAE patients and physicians should be alert of the occurrence and emergency treatment of laryngeal edema. We recommend that C4 alone should not be used to exclude the diagnosis of HAE-C1INH. The laboratory work-up should also include C1 inhibitor levels and C1INH function analysis.

Key words: *hereditary angioedema, attack localization, C4, laryngeal edema, erythema marginatum*

Abbreviations: *hereditary angioedema (HAE), C1 inhibitor (C1INH), hereditary angioedema with C1-inhibitor deficiency (HAE-C1INH), hereditary angioedema with normal C1 inhibitor (HAE-nlC1INH), standard deviation (SD)*

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Özet

Amaç Herediter anjiyoödem (HA) tekrarlayan anjiyoödem atakları ile karakterize otozomal dominant nadir bir hastalıktır. HA, C1-inhibitörü (C1INH) eksikliği ile seyreden (C1INH-HA) ve C1-inhibitörü normal HA (nlC1INH-HA) olarak sınıflandırılır. Ataklar sırasında üst solunum yolları, gövde, gastrointestinal sistem, genital bölge ve ekstremitelerde tekrarlayan şişlikler oluşur. Larinks ödemi uygun tedavi edilmediği takdirde ölüme yol açabilir. Bu çalışmada C1INH-HA hastalarının atak lokalizasyonları ile kompleman parametreleri arasındaki ilişki incelenmiştir.

Yöntem Ege Üniversitesi Tıp Fakültesi'nde izlenmekte olan C1INH-HA hastaları dahil edildi. nlC1INH-HA hastaları çalışmaya alınmadı. Klinik kayıtlara ilişkin veriler retrospektif olarak elde edildi. Sosyodemografik veriler, hastalığın başlangıç yaşı, yıllık atak sıklıkları, atak lokalizasyonu ve kompleman parametreleri kaydedildi.

Bulgular Çalışma grubunda 100 hasta mevcuttu. Hastaların %54'ü kadındı. Hastaların çoğunda Tip 1 C1INH-HA (%87) vardı. Ortalama hastalık başlangıç yaşı 12.01 ±7.04 yıldı. Plazma C4 düzeyleri sekiz hastada (%8.16) normaldi. En sık tutulan lokalizasyonlar ekstremiteler (%91), gastrointestinal sistem (%89) ve genital bölge (%85) idi. Yüz bölgesinde atak geçirme ve eritema marginatuma sahip olma ayrı ayrı analiz edildiğinde her ikisi de laringeal ödem varlığı ile ilişkili bulunmuştur. Eritema marginatumu olan hastaların % 83.8' inde (P=0.010), yüz atakları olan hastaların % 75.9' unda (P<0.001) laringeal ödem görülmüştür.

Sonuç Eritema marginatum ve laringeal ödem arasındaki ilişki önceki çalışmalarda bildirilmemiştir. Laringeal atakların öngörülemeyen ve ölümcül doğası nedeniyle, tüm HA hastaları ve doktorlar laringeal ödemin gelişimi ve acil tedavisi konusunda gerekli bilgi ve beceriye sahip olmalıdır. C1INH-HA tanısını dışlamak için tek başına C4 kullanılmaması önerilir. Laboratuar analizleri C1INH düzeyleri ve C1INH fonksiyon analizini de içermelidir.

Anahtar kelimeler: *herediter anjioödem, atak lokalizasyonu, C4, larinks ödemi, eritema marginatum*

Kısaltmalar: *Herediter anjioödem (HA), C1 inhibitor (C1INH), C1 inhibitör eksikliği olan herediter anjioödem (HAE-C1INH), normal C1 inhibtör düzeyleri ile seyreden herediter anjioödem (HAE-nlC1INH)*

Introduction

Hereditary angioedema (HAE) was first described clinically in the 19th century.[1] It is characterized by recurrent angioedema episodes without wheals. Its prevalence is reported from 1:10 000 to 1:150 000 in the literature.[2-4] HAE is classified into HAE with C1 inhibitor deficiency (HAE-C1INH) and HAE with normal C1 inhibitor levels (HAE-nlC1INH) (Table 1). HAE-C1INH is inherited by autosomal dominant SERPING1 gene mutations with incomplete penetrance. HAE-nlC1INH can be due to the mutations in FXII, plasminogen, angiopoietin-1, and kininogen-1 genes.[5-9]

Table 1. Hereditary angioedema classification

HAE with C1-INH deficiency
Type I: C1-INH level is low
Type II: C1-INH dysfunction
Mutations in SERPING1 gene
HAE with normal C1-INH
C1-INH function is normal
Mutations in FXII, plasminogen, angiopoietin-1 and kininogen-1 genes

The deficiency of C1 inhibitor (C1INH) results in uncontrolled activation of the complement system and the release of bradykinin. Bradykinin increases vascular permeability which results in results in recurrent angioedema episodes.[10,11] The angioedema episodes last for 2-5 days. It may involve the face, larynx, upper airways, trunk, gastrointestinal system (GIS), genital area, and extremities. The angioedema attacks are disabling, and laryngeal edema can lead to asphyxiation and death if it is not treated successfully.[12,13] The burden of hereditary angioedema impairs quality of life of the patients.[14]

We aim to investigate the association between attack localizations and complement parameters of HAE-C1INH patients.

Methods

One-hundred patients diagnosed with HAE-C1INH at Ege University Faculty of Medicine, Allergy and Clinical Immunology Clinic were included in the study. Patients with HAE-nlC1INH were excluded. Clinical data, including sociodemographic data, age at disease onset, annual attack frequencies, attack localizations and complement parameters were obtained retrospectively from the hospital database.

Complement Studies

C4 (reference range, 10-40 mg/dL) and C1 inhibitor antigen levels (reference range, 21-39 mg/dL) were analyzed by immunonephelometry (Siemens, Marburg, Germany), and C1 inhibitor function levels (reference range, 70-130%) were measured by chromogenic assay (Berichrom Siemens, Marburg, Germany).

Statistical Analysis

Quantitative data were described as mean with standard deviation (SD) and median with minimum-maximum values, while qualitative data were described as observed frequencies and percentages. *Shapiro-Wilk test* was used for the normality analysis of quantitative variables in groups. According to the test result and the exploratory data analysis, parametric or non-parametric suitable statistical tests were performed. An independent samples t-test or its non-parametric alternative, *Mann-Whitney U test* was used to compare two groups for a quantitative variable. A *chi-square test* was used for analyzing the association between qualitative variables. All statistical analysis were performed with the statistical package (SPSS Inc., version 25.0). The significance level was accepted at $P<0.05$

Results

Fifty-four (54%) out of 100 patients were female. The mean age was 42.96 ±14.14 in females and 42.0 ±15.01 in males. The majority of patients were HAE-C1INH type I (n=87, 87%).

The mean age at disease onset was 12.01 ±7.04 years, and the average delay in diagnosis was 21.63 ±13.24 years. Plasma C4 levels were in normal (reference range:10-40 mg/dL) in eight patients (8.16%). All of these eight patients had a low C1INH function with a median of 29.15% [0%-56.5%] (reference range:70-130%). The median C1INH function of all patients was 12.9% [0%-78%]. C1INH levels in HAE-C1INH type I and type II patients were 5.4 [2-16] vs. 45 [33.2-64.6], respectively.

Table 2. Age at disease onset, attack frequency and complement parameters of the HAE-C1INH type I and type II patients

	Type I (n=13)		Type II (n=87)		*P*
	Mean (±SD)	Median [Min-Max]	Mean (±SD)	Median [Min-Max]	
Age at disease onset (years)	12.33±7.27	11 [2-35]	9.85±4.83	10 [4-18]	0.236
Delay in diagnosis (years)	21.64±13.66	20 [0-57]	21.54±10.43	19 [9-44]	0.979
C1INH function (%)	14.96±13.0	12.4 [0-78]	17.71±10.70	14 [5.10-39.10]	0.271
C1INH (mg/dL)	5.99±3.10	5.4 [2-16]	43.52±8.42	45 [33.2-64.6]	NA*
C4 (mg/dL)	6.28±2.56	6 [2-18]	6.01±1.99	6 [2.08-10]	0.781
Attack frequency (annual)	27.93±23.61	24 [1-120]	33.0±30.69	24 [1-100]	0.762

*Since C1INH levels are normal in HAE-C1INH type II patients by definition, no statistical comparison was made for C1-INH

Age at disease onset, delay in diagnosis, C1INH function, and C4 levels and annual attack frequency were compared between HAE-C1INH type I and type II patients and the results showed that there was no statistical significance (*P*>0.05) (Table 2).

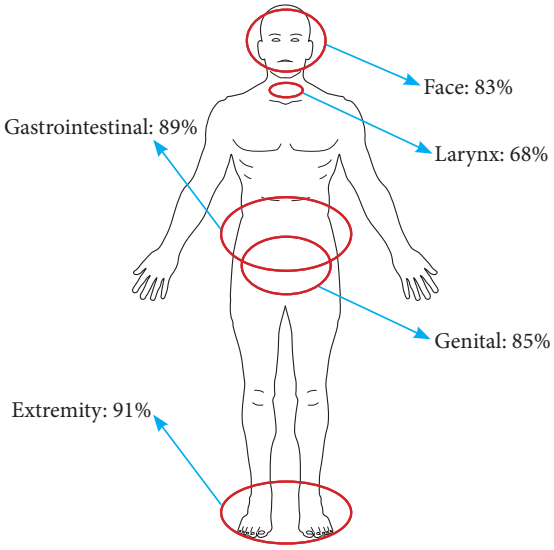

Fig. 1. The percentages of attack localizations

When the localization of attacks is examined, the most frequent attack localizations is respectively; 91% is extremities, 89% is gastrointestinal tract, and 85% is genital area. The facial involvement rate was 83%, and the laryngeal involvement rate was 68% (Fig. 1).

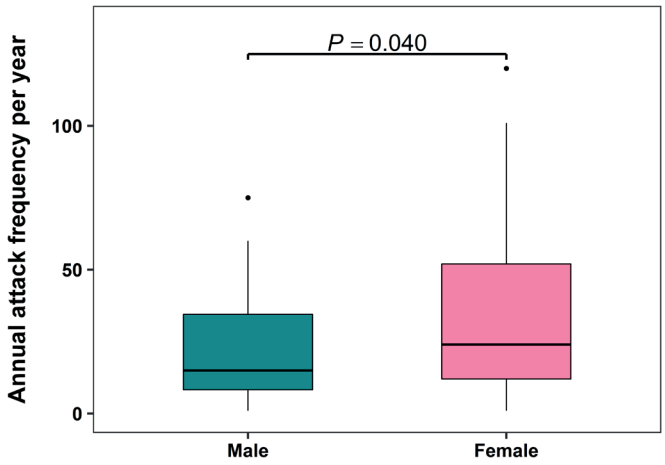

Fig. 2. The comparison of the frequencies of annual attacks according to gender
The box plot shows the differences and the distribution of annual attack frequency of female and male patients. The horizontal lines in the box plot indicate 75th percentile, median, and 25th percentile, respectively, from top to bottom. Points represent potential outliers in the data.

The annual attack frequency was higher in female patients than males (24 [1-120] vs. 15 [1-75], P=0.040) (Fig. 2).

For each attack localization, there was no statistically significant difference in C4 levels, C1INH function, and C1INH levels between those who had attacks and those who did not (*P*>0.05) except that C4 levels were lower in patients with the gastrointestinal attack (*P*=0.026) (Table 3).

The results depict that there was a significant association between laryngeal edema and both of the erythema marginatum and facial attacks (*P*=0.010 and *P*<0.001, respectively) (Fig. 3). 83.8% of the patients with erythema marginatum and 75.9% of the patients with facial attacks also had laryngeal edema.

Patients who had a family history of fatal asphyxiation due to laryngeal edema had a higher laryngeal edema rate (77.5% vs. 52.2%, respectively, and *P*=0.015).

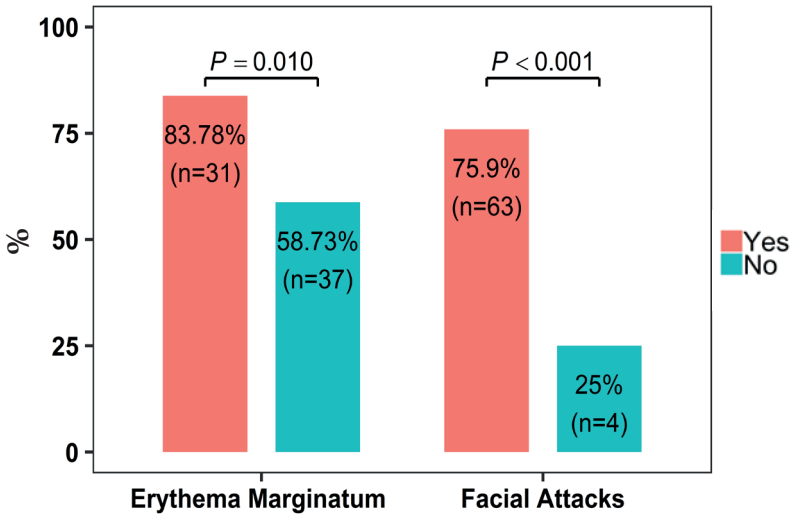

Fig. 3. The comparison of the presence of laryngeal edema in patients with or without erythema marginatum and facial involvement

Discussion

The distribution of type I (87%) and type II (13%) patients were similar to previous studies, mainly type I.[15,16] The average delay in diagnosis was 21.63 years in our research. In the Italian cohort, the delay in diagnosis was 12.8 years.[15] The other surveys in France,

Table 3. The complement parameters according to attack localizations

Attack localization		C4 (mg/dL)			C1INH function (%)			C1INH (mg/dL)		
		Mean ±SD	Median [Min-Max]	*P*	Mean ±SD	Median [Min-Max]	*P*	Mean ±SD	Median [Min-Max]	*P*
Face	Yes (n=83)	6.28 ±2.56	6 [2-18]	0.883	15.71 ±13.53	12.6 [0-78]	0.948	6.04 ±3.22	5.25 [2-16]	0.752
	No (n=16)	6.16 ±2.06	6 [4-11]		13.35 ±7.56	14 [0-29.30]		5.92 ±2.60	5.7 [2-11.9]	
Larynx	Yes (n=68)	6.11 ±2.25	6 [2-16]	0.484	14.30 ±11.25	12 [0-56.50]	0.369	5.99 ±3.10	5 [2-16]	0.884
	No (n=32)	6.51 ±2.93	6 [2-18]		17.34 ±15.27	14.30 [0-78]		6 ±3.17	5.85 [2-14]	
Trunk	Yes (n=40)	5.86 ±2.52	6 [2-16]	0.085	13.11 ±10.91	10 [0-39.10]	0.156	5.75 ±2.83	5.4 [2-16]	0.821
	No (n=59)	6.54 ±2.44	6 [4-18]		16.74 ±13.73	14.50 [0-78]		6.18 ±3.29	5.4 [2-14.80]	
Extremity	Yes (n=91)	6.04 ±2.09	6 [2-16]	0.097	14.91 ±12.02	12.95 [0-78]	0.691	5.82 ±2.75	5.4 [2-16]	0.710
	No (n=7)	9.14 ±4.85	6 [5-18]		20.09 ±19.81	16.30 [0-56.50]		8.22 ±5.76	5.85 [2.90-14.80]	
GIS	Yes (n=89)	6.03*±2.23	6 [2-16]	0.026	15.69 ±13.04	14 [0-78]	0.363	5.88 ±3.01	7 [2-14]	0.482
	No (n=11)	7.91 ±3.67	6 [6-18]		12.27 ±9.82	10 [0-29.30]		6.80 ±3.75	5.32 [2-16]	
Genital	Yes (n=77)	5.98 ±2.15	6 [2-16]	0.880	14.75 ±12.42	12 [0-78]	0.694	5.89 ±2.96	5.1 [2-16]	0.559
	No (n=13)	6.20 ±2.30	6 [4-13]		17.42 ±15.59	16.30 [0.20-56.50]		5.49 ±3.05	5.4 [2.90-14.80]	

*Patients having gastrointestinal (GIS) attacks were found to have lower C4 values (***P***=0.026). In other attack localizations, no statistically different C4 levels were found

Spain, and Denmark, the mean delay in diagnosis was 12, 13.1, and 16.3 years, respectively.[5,17,18] Delays in diagnosis are particularly crucial because of the potentially fatal laryngeal edema risk of undiagnosed patients. Misdiagnoses and diagnostic delays were stated as negative factors influencing the patients' quality of life.[19] Bork et al. reported that women have a more severe course of disease than men.[16] Similarly, in our study, the frequency of annual attacks was higher in female patients than in male patients.

We found that patients with erythema marginatum episodes, either as a prodromal sign or as an isolated finding, are more likely to have laryngeal edema. In previous studies, this association was not described. Due to the unpredictable and potentially fatal course of the laryngeal attacks, all HAE patients and the physicians should be alert of the occurrence and emergency treatment of laryngeal edema.

Agostoni and Cicardi described the rate of abdominal attacks as 73% and laryngeal edema as 48%.[20] Bork et al reported facial attacks as 75.6% and genital attacks as 62.7% .[16]

In our study, the frequency of genital attacks (85%) and facial attacks (83%) was higher than the previous studies. The awareness of HAE is increasing, and more patients with milder symptoms have the opportunity to be diagnosed. Patients with the most feared attack localizations like facial and genital areas may have a higher chance of being diagnosed.

Measurement of C4 levels is used for HAE-C1INH

screening.[21,22] Zanichelli et al. stated that the C4 level was low in 96% of patients, and normal C4 values may eliminate the diagnosis of HAE-C1INH with an error probability of less than 0.05 .[15] According to a multicenter study, the combined use of antigenic C4 and C1INH function was described as a 98% specificity for HAE-C1INH with a negative predictive value of 96%.[23] In a controlled study, the sensitivity of low C4 levels for the diagnosis of HAE was 81% .[24] In our study, 91.84% of well established HAE-C1INH patients had low C4 levels. The assays to measure C4 are widely available and relatively inexpensive. We recommend that C4 alone should not be used to exclude the diagnosis of HAE-C1INH, especially between attacks. The laboratory work-up should also include C1INH function analysis according to the clinical situation of the patients.

In our study, the complement levels and attack localizations were not found to be correlated, except gastrointestinal attacks. Patients having gastrointestinal attacks had lower C4 values (P=0.026).

In conclusion, the presence of erythema marginatum could be a sign of laryngeal involvement in HAE-C1INH patients as well as facial edema. There is no association between the complement levels and attack localizations, at least during the off-attack period. In addition, nearly 8% of HAE-C1INH patients had normal C4 levels in symptom-free periods. To have a correct diagnosis, C1INH function should be added to the diagnostic analysis.

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