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Original Article

Do Hormonal Disorders Contribute to the Pathology of Hereditary Angioedema?

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ABSTRACT

Background Hereditary angioedema (HAE) is an autosomal dominant disorder characterized by recurrent episodes of angioedema without urticaria or pruritus. In this study, we compared the levels of anabolic hormones, such as insulin, insulin-like growth factor, growth hormone, and thyroid hormones (thyroid-stimulating hormone [TSH], triiodothyronine [T3], and thyroxine [T4]), and the levels of hormones that are considered catabolic, such as adrenocorticotrophic hormone (ACTH) and cortisol, between HAE patients and controls. We also discussed the contribution of these hormones to the pathophysiology of HAE.

Material and Methods The study included 18 patients (9 diagnosed with HAE type 1 and 9 with HAE type 2) who were followed in the immunology and allergy clinic between January 2013 and January 2020. The control group comprised 28 age- and gender-matched healthy control subjects. For determination of hormone levels enzyme standard radioimmunoassay, immunometric and immunoluminometric assays were used.

Results The HAE type 1, HAE type 2, and healthy control groups showed no significant differences in insulin, insulin-like growth factor, ACTH, cortisol, TSH, or T4 levels. The C-peptide and T3 levels were significantly different between the groups (p=0.011 and p=0.027, respectively). Post-hoc pairwise comparison revealed no significant difference in C-peptide level among the groups, but a significant difference in the T3 level was detected between HAE type 1 patients and controls (p=0.029).

Conclusions Although no significant differences were observed in other anabolic hormone levels between the controls and HAE patients, T3 levels were significantly lower in type 1 HAE patients. Close monitoring of low T3 levels is required, particularly in patients with type 1 HAE.

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Introduction

Hereditary angioedema (HAE) is an autosomal dominant disorder characterized by recurrent episodes of angioedema without urticaria or pruritus. Attacks often involve the skin, upper respiratory mucosa, and gastrointestinal tract. Angioedema attacks are self-limiting and the sufferer completely returns to normal within 2-5 days. However, fatal asphyxia can occur due to laryngeal involvement.[1,2] During an attack, plasma bradykinin levels rise well above normal, and the development of angioedema has been attributed to the increase in bradykinin.[3] Agents such as antifibrinolytics (tranexamic acid), partial androgen analogs (danazol), plasma-derived C1 inhibitor concentrates, and humanized plasma kallikrein monoclonal antibodies are used as prophylactic treatment for the disease.[4-7] Plasma-derived and recombinant C1 esterase inhibitor concentrates, bradykinin b2 receptor antagonists, and kallikrein inhibitors can be used to treat an acute attack.[8] Danazol is a partial androgen that has been used successfully for many years to treat patients with HAE.[9,10] In animal experiments, danazol prevents attacks by increasing liver production of the C1 esterase protein.[11,12] Other hormones increase the synthesis of serum proteins from the liver during the pathogenesis of HAE, and may be useful in the treatment of the disease. Although activation of factor XII and plasma prekallikrein on the endothelial cell surface is important in the initiation of attacks, information is limited as to why HAE patients show deficits in the synthesis of the C1 esterase protein, and whether they have adequate levels of anabolic hormones that aid in the synthesis of the C1 esterase protein by the liver. In this study, we compared the levels of anabolic hormones, such as insulin, insulin-like growth factor, growth hormone, and thyroid hormones (thyroid-stimulating hormone [TSH], triiodothyronine [T3], and thyroxine [T4]), and catabolic hormones, such as adrenocorticotrophic hormone (ACTH) and cortisol, between HAE patients and controls. We also discuss the contribution of these hormones to the pathophysiology of HAE.

Material and Methods

The study included 18 patients (9 diagnosed with HAE type 1 and 9 with HAE type 2) followed in the immunology and allergy clinic between January 2013 and January 2020. We also included 28 age- and gender-matched subjects as controls. Patients with known hypothyroidism or hyperthyroidism who took medication, had another chronic disease that may cause euthyroidism, had a diagnosis of widespread inflammatory disease or diabetes mellitus, or received other medical treatment were excluded from the study. The study protocol was approved by the local ethics committee (decision no: 2018/1576, date: 16.10.2018), and written informed consent was obtained from all patients.

All HAE patients were under on-demand treatment and none were receiving prophylactic treatment, such as tranexamic acid or danazol, for HAE. Blood samples were taken from all HAE patients when they were asymptomatic for HAE attacks.

Venous blood samples were drawn for biochemical analyses after at least 10 h of fasting early in the morning (7.00 am). All biochemical analyses were performed in the central biochemistry laboratory of the Meram Faculty of Medicine. Complete blood counts were performed with the Cell Dyn 3700 device (Abbott Laboratories, Abbott Park, IL, USA). Serum C4 levels were measured with the Advia 2400 Clinical Chemistry System (Siemens, Tarrytown, NY, USA) using a colorimetric method. Serum C1 esterase inhibitor levels were measured with the Siemens BN II/BN ProSpec system and a nephelometric assay. Serum C1 esterase inhibitor function was assessed by the chromogenic method using the Stago Compact Max device (Stago, Parsippany, NJ, USA).

Concentrations of insulin, c-peptide and ACTH were assessed using standard radioimmunoassay (RIA) (Pharmacia Insulin RIA 100, Pharmacia & Upjohn, Inc., Uppsala, Sweden; Lumitest ACTH, Brahms Diagnostica GmbH, Berlin, Germany). For determination of cortisol, TSH, free T3, and free T4, enzyme immunometric and immunoluminometric assays were used, respectively (Enzymun-Test Cortisol ES 300 and Elecsys, Roche Molecular Biochemicals, Mannheim, Germany). All samples were measured

in duplicate in the same assay. Serum insulin-like growth factor (IGF-1) level was determined using an immunofluorometric assay with acid-ethanol serum extracts.

Statistical analysis

The analysis was performed with IBM SPSS Statistics software (ver. 22.0; IBM Corp., Armonk, NY, USA). Normally distributed parameters are presented as mean±standard deviation, and skewed parameters as medians (interquartile range). Descriptive data are presented as frequencies and percentages, and were compared using the chi-square test. Baseline characteristics were compared using the independent Student's *t*-test, Mann-Whitney rank-sum test, Fisher's exact test, or chi-square test, as appropriate. We used one-way analysis of variance for analyzing normally distributed parameters with homogeneity of variances. We used the Kruskal-Wallis method if a parameter was not normally distributed or heterogeneity was detected. Tamhane's T2 test was used for the post-hoc analysis. A p-value >0.05 was considered significant.

Results

In total, 18 HAE patients (12 females and 6 males) and 28 age- and gender-matched healthy subjects (18 females and 10 males) were included in the study. In the HAE group, nine patients with a diagnosis of type 1 HAE, and nine with type 2 HAE, were followed up. The demographic and laboratory characteristics of the patients are summarized in Table 1.

The average ages of the HAE and control groups were 36.33±11.81 and 38.07±12.21 years, respectively. No differences in age or gender were observed between the patients and controls (p=0.634 and p=0.747, respectively). Although the insulin, IGF-1, growth hormone, ACTH, cortisol, TSH, and T4 levels tended to be lower in HAE patients than controls, the differences were not significant (*Figure 1*). However, a significant difference in C-peptide levels was observed between the HAE patients and controls (p=0.030). In addition, the T3 levels were significantly lower in the HAE patients (p=0.130) (*Table 2*) (*Figure 2*).

No significant differences in insulin, IGF-1, ACTH, cortisol, TSH, or T4 levels were detected among the HAE type 1, HAE type 2, and control groups. Significant differences in C-peptide and T3 levels were observed among the groups (p=0.011 and p=0.027, respectively) (*Table 3*). Post-hoc pairwise comparisons revealed no significant difference in C-peptide levels among the groups, but a significant difference in T3 levels was observed between HAE type 1 patients and controls (p=0.029) (*Table 4*).

Table 1. Demographic and laboratory parameters of the hereditary angioedema patients (n: 18).

Parameters	Values
Age (years)	36.33±11.81
Females n (%)	12 (66.7)
HAE type I n (%)	9 (50)
HAE type II n (%)	9 (50)
Consanguinity n (%)	6 (33.3)
C1 esterase inhibitor level (mg/dL)	11.00 (3-50)
C1 esterase inhibitor activity (%)	14 (3-171)
Age of onset of symptoms (years)	9 (2-56)
Age at diagnosis, years	20.50±12.71
Diagnostic delay, years	3.50 (0–34)
Neutrophil count at diagnosis (mm^3)	5,488.89±1,681.00
Lymphocyte count at diagnosis (mm^3)	2,007.78±667.92
Platelet count at diagnosis (mm^3)	281,388.89±92,430.67
ANA positivity n (%)	3 (16.67)
C4	0.06 (0.01-0.23)

HAE: hereditary angioedema, C1: complement factor 1, ANA: antinuclear antibody.

Discussion

HAE is a rare autosomal dominant disease characterized by a C1 esterase inhibitor deficiency and/or decreased activity. In our study, a significant difference in the T3 level was observed between HAE patients and healthy controls, due to the difference between type 1 HAE patients with a C1 esterase inhibitor deficiency and controls. The

Table 2. Comparison of clinical parameters of hereditary angioedema and control patients.

Parameters	HAE (n: 18)	Controls (n: 28)	P value
Age (years)	36.33±11.81	38.07±12.21	0.634
Females n (%)	12 (66.7)	18 (72)	0.747
Glucose (mg/dL)	87.50±11.03	98.12±9.97	0.934
Insulin (mU/L)	11.25 (4.92-48.22)	14.03 (2-81.80)	0.350
C-peptide (ng/mL)	2.95 (1.81-9.72)	2.51 (0.39-7.05)	0.030
IGF-1 (ng/mL)	163.31±68.01	180.01±57.58	0.260
Growth hormone (ng/mL)	0.24 (0.04-3.15)	0.35 (0.05-8.24)	0.866
ACTH (pg/mL)	17.64 (10.48-31.03)	17.73 (6.20-64.20)	0.620
Cortisol (mcg/dL)	11.33±4.26	14.47±6.03	0.045
TSH (mU/L)	1.62 (0.77-4.86)	1.65 (0.53-5.27)	0.311
Free T3 (ng/L)	3.04±0.34	3.30±0.31	0.013
Free T4 (ng/dL)	1.29 (0.023-0.151)	1.34 (1.10-14.0)	0.131

Data were given as mean±SD or median (min-max). HAE: hereditary angioedema, IGF-1: insulin-like growth factor 1, ACTH: adrenocorticotropic hormone, TSH: thyroid-stimulating hormone, T3: triiodothyronine, T4: thyroxine.

Table 3. Hereditary angioedema type I, type II, and control patients' demographic and laboratory parameters.

Parameters	HAE type 1 (n: 9)	HAE type 2 (n: 9)	Controls (n: 18)	P value
Age (years)	37.67±10.89	35.00±13.19	38.07±12.21	0.804
Females n (%)	6 (66.7)	6 (66.7)	6 (64.3)	0.986
Glucose (mg/dL)	85.07±12.28	90.63±9.50	88.12±10.27	0.525
Insulin (mU/L)	11.29 (4-36.68)	11.20 (5.35-48.22)	14.03 (2-81.80)	0.637
C-peptide (ng/mL)	2.95 (1.87-5.91)	2.94 (1.81-9.72)	2.51 (0.39-7.05)	0.011
IGF-1 (ng/mL)	159.53±45.63	167.09±87.84	180.01±57.58	0.657
Growth hormone (ng/mL)	0.16 (0.4-3.15)	0.28 (0.04-1.40)	0.35 (0.05-8.24)	0.523
ACTH (pg/mL)	17.10 (10.48-31.03)	18.17 (11.13-27.49)	17.73 (6.20-64.20)	0.884
Cortisol (mcg/dL)	11.92±4.80	10.74±3.85	14.47 ± 6.03	0.160
TSH (mU/L)	1.61 (0.82-2.52)	1.65 (0.77-4.86)	1.65 (0.53-5.27)	0.559
Free T3 (ng/L)	2.97±0.34	3.11±0.34	3.30±0.31	0.027
Free T4 (ng/dL)	1.19 (1.04-1.45)	1.33 (1.03-1.50)	1.34 (1.10-14.00)	0.184

Data were given as mean±SD or median (min-max). HAE: hereditary angioedema, IGF-1: insulin-like growth factor 1, ACTH: adrenocorticotropic hormone, TSH: thyroid-stimulating hormone, T3: triiodothyronine, T4: thyroxine.

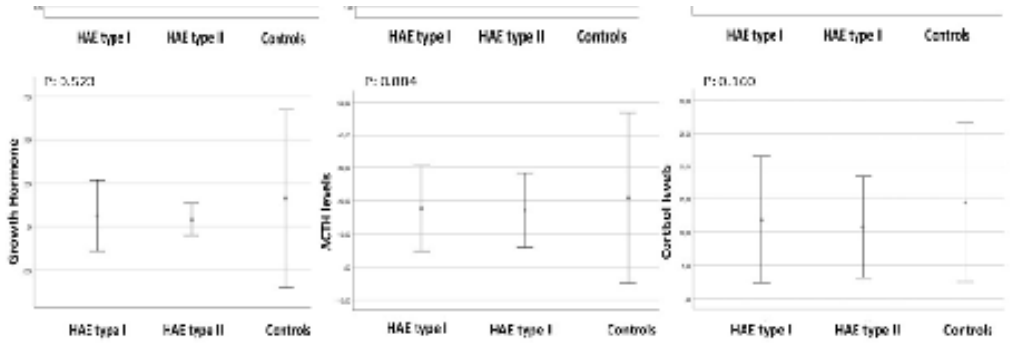

Figure 1. Comparison of hormone levels among the hereditary angioedema type 1, hereditary angioedema type 2 and control groups.

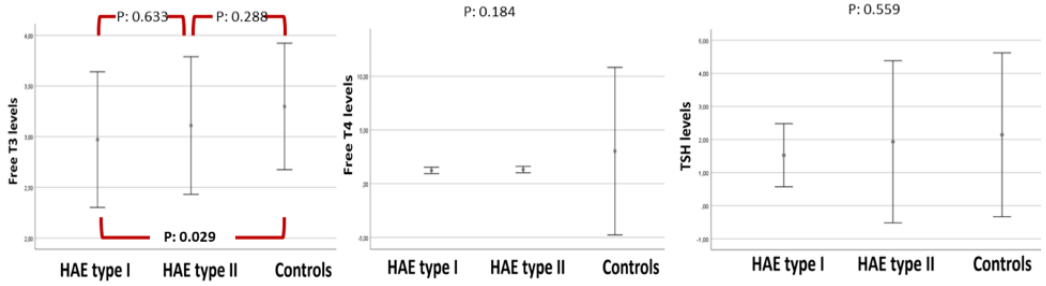

Figure 2. Comparison of thyroid hormone levels among the hereditary angioedema type 1, hereditary angioedema type 2 and control groups.

Table 4. Post-hoc analysis of HAE patients according to T3 and C-peptide levels.

Parameters			P value
T3	HAE type I	HAE type II	0.633
		Controls	0.029
	HAE type II	HAE type I	0.633
		Controls	0.288
C-peptide	HAE type I	HAE type II	0.907
		Controls	0.185
	HAE type II	HAE type I	0.907
		Controls	0.326

HAE: hereditary angioedema, T3: triiodothyronine.

levels of other anabolic hormones, such as insulin, IGF-1, growth hormone, TSH, and T4, tended to be lower in HAE patients than control groups, although the differences were not significant.

Thyroid hormones control and regulate the synthesis of many plasma proteins[13-15], including transferrin, prothrombin and angiotensinogen, as well as complement, fibrinogen, and lipoproteins. Zhang et al.[16] showed that thyroid hormone and complement levels were correlated in patients with multiple sclerosis. Karkhaneh et al.[17] reported that serum T3 and T4 levels were correlated with complement levels in normal-weight humans. Czaller et al.[18] reported lower free T3 and free T4 levels in patients with type 1 HAE compared to controls. In the same study, free T4 levels were lower in patients who had more versus less frequent

HAE attacks. These findings suggest that thyroid hormones have an effect on complement in many diseases, and may also play a role in the course of HAE, which is considered a complement system disease.

Thyroid hormones also have many effects on the coagulation and fibrinolytic systems.[19-21] Numerous studies have examined the relationship between histamine-mediated angioedema and thyroid hormone disorders[15,22-25], but few have investigated the relationship between HAE and thyroid hormones. Moreover, these studies mostly examined the relationships of hyperthyroidism, hypothyroidism, and thyroiditis with HAE attacks.[26,27] Thyroid disorders are among the most common autoimmune disorders in type 1 HAE patients.[28] Liu et al.[29] reported a case of coexisting Graves' disease and type 1 HAE. Farkas et al.[26] showed that the frequency of attacks is lower in HAE patients taking anti-thyroid drugs or thyroid hormone replacement therapy. The findings of our study and those of Farkas et al.[26] suggest that the metabolic effects of thyroid hormones are involved in the pathogenesis of HAE.

Type 1 HAE progression is associated with a low C1 esterase inhibitor level, and type 2 HAE progression with dysfunction in the C1 esterase inhibitor.[30] The finding that the T3 level was significantly different between our type 1 (but not type 2) HAE patients and controls supports our hypothesis that T3 may affect the course of the disease by synthesizing the C1 esterase inhibitor.

In the most recent primary immunodeficiency disease (PID) classification system, HAE was included in the complement deficiency subclass of primary immunodeficiencies, and in the immunodeficiency group with susceptibility to infections.[31] Although frequent infections are not the main clinical feature of HAE, recurrent angioedema attacks in these patients may cause low T3 by including euthyroid sick syndrome, which is seen during chronic and serious diseases.

The main limitations of this study were its single-center design and relatively small population. The absence of a patient group taking a normal C1 inhibitor, and of patients evaluated for mutations known to be involved in the etiology of HAE (such as SERPING, FXII, angiopoietin, and plasminogen mutations), are further limitations.

Conclusions

We hypothesized that the levels of anabolic hormones might be lower in the HAE patient group than controls, based on long-term prophylaxis with danazol, and the increased expression of complement proteins and many serum protein syntheses due to the anabolic effects of danazol. Although no significant difference was observed between the controls and HAE patients in of the levels of other anabolic hormones, the T3 levels were significantly lower in type 1 HAE patients than controls. Close monitoring of low T3 levels is required, particularly in patients with type 1 HAE. Larger studies are needed to assess the effects of T3 replacement on C1 esterase inhibitor levels and attack frequency in euthyroid HAE patients.

Conflict of interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

Local ethics committee approved the study protocol.

Authors' Contribution

Study Conception, Design, Supervision, Critical Review, Manuscript preparing: GA, HO, IB, FC, EY, SA, AZC; Literature Review: HO; Statistical Analysis and/or Data Interpretation: IB.

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