

Association between thyroid autoimmunity and recurrent angioedema in children

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ABSTRACT

Background: The association between thyroid autoimmunity (TA) and idiopathic isolated angioedema (or angioedema without urticaria) has not been evaluated in either children or in adults up until now. We, therefore, aimed to investigate underlying or concomitant TA and/or autoimmune thyroid disease in children diagnosed with recurrent idiopathic angioedema.

Methods: Children who were consecutively diagnosed with recurrent idiopathic histaminergic acquired angioedema (IH-AAE) between January 2011 and January 2014 constituted the case group. A standard diagnostic and therapeutic algorithm was applied to all the patients with recurrent IH-AAE. Thyroid autoantibodies and thyroid function tests were measured in all the patients with recurrent IH-AAE and in healthy control groups. Prophylaxis with an antihistamine was started for patients with frequently recurrent IH-AAE.

Results: Eighty consecutive children with recurrent IH-AAE (49 boys; median age, 8.3 years) and 80 healthy children (39 boys; median, 8 years) were enrolled in this prospective, case-control study ($p > 0.05$ for age and sex). The IH-AAE group was significantly different than the control group with respect to TA (13.7% versus 2.5%, respectively; $p = 0.009$) but was similar with respect to autoimmune thyroid disease (3.7% versus 0%, respectively; $p = 0.2$). The median follow-up of the recurrent IH-AAE group was 34 months (range, 12–45 months). Patients with recurrent IH-AAE with and those without TA were not different with respect to either the need or the duration of antihistamine prophylaxis ($p > 0.05$ for both).

Conclusions: Recurrent IH-AAE may be related to or associated with TA and/or autoimmune thyroid diseases in some children. However, exploring to see whether this association is a causal link or just an epiphenomenon deserves further investigation and longer follow-ups.

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Urticaria and angioedema commonly occur together but may also occur separately.¹ Recently, awareness about angioedema without urticaria has increased.^{2,3} Also, a position paper on the classification, diagnosis, and approach for the treatment of angioedema has been published.⁴ Most of the time the final diagnosis of patients with angioedema and those without urticaria was found to be idiopathic after the exclusion of hereditary forms both in children and in adults.^{2,3,5,6} In addition, most cases of chronic urticaria (CU) have been considered to be idiopathic.¹ The association between CU and thyroid autoimmunity (TA) has been investigated for many years.^{7–9} Although a recent large population study in Israel found a strong association between CU and major autoimmune diseases, especially autoimmune thyroid diseases, this is still an ongoing debate.^{9–12} However, the association

between TA and idiopathic angioedema has not been evaluated in either children or adults up until now. We, therefore, aimed to investigate underlying or concomitant TA and/or autoimmune thyroid disease in children diagnosed with recurrent idiopathic angioedema and to follow up on cases related to these conditions.

MATERIALS AND METHODS

Patients

This prospective study was conducted in the outpatient clinic of the Pediatric Allergy and Asthma Unit, Gazi University Hospital. Children who were consecutively diagnosed with recurrent idiopathic histaminergic acquired angioedema (IH-AAE) between January 2011 and January 2014 constituted the case group. Demographic characteristics and information regarding atopic disease and family history were obtained. The control group included healthy children without angioedema, urticaria, thyroid gland, or autoimmune disease. Both groups were compared with respect to the presence of TA and autoimmune thyroid disease. The Gazi University Faculty of Medicine Ethics Committee approved the study, and written informed consent was

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The authors have no conflicts of interest to declare pertaining to this article

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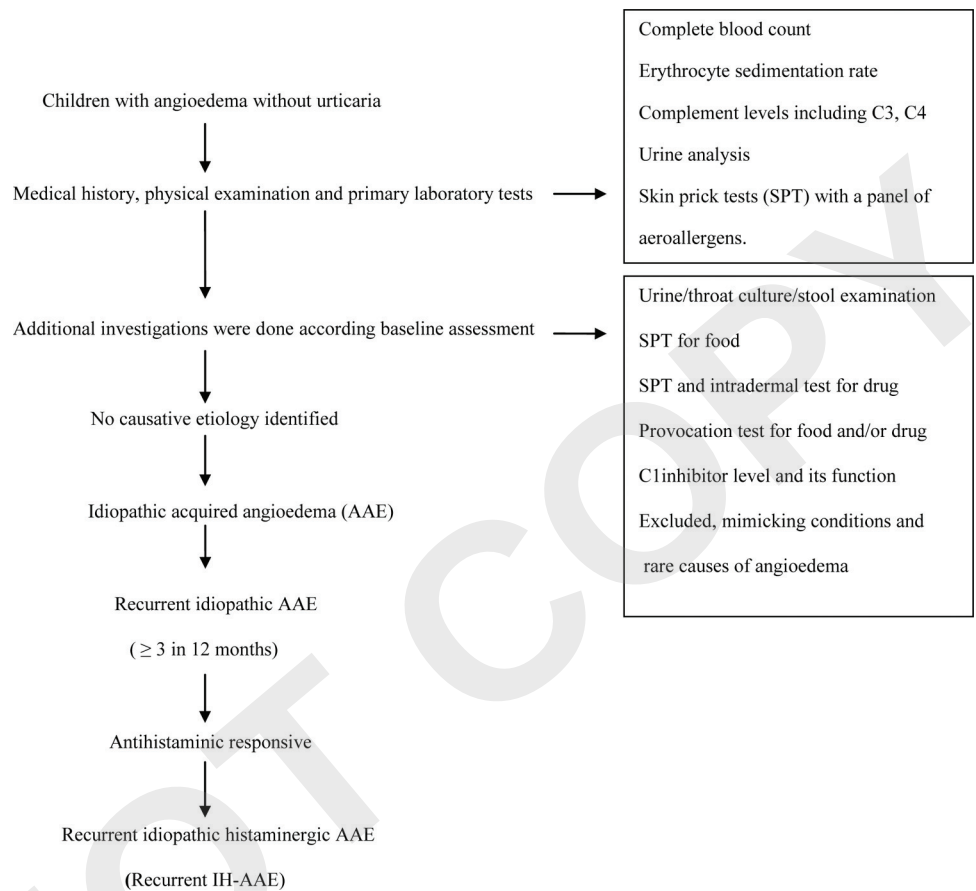


Figure 1. Diagnostic algorithm with recurrent IH-AAE.

obtained from all the participating children and/or their parents.

Author contributions included the following: H. Ertoý Karagol participated in the development of the protocol, had primary responsibility for assessment of the participants in the study center, and prepared the manuscript with A. Bakirtas. A. Bakirtas had primary responsibility for protocol development and outcome assessment. She prepared the manuscript with H. Ertoý Karagol. O. Yilmaz, E. Topal, and A. Bideci were responsible for the assessments of participants in the study.

Definitions

Angioedema was defined as a asymmetric, nondependent, and nonpitting swelling of the deeper layers of the skin and mucous membranes that resolves without scarring or discoloration. Angioedema that is not associated with urticaria is defined as angioedema without urticaria. If no underlying etiologic factors are detected, then angioedema without urticaria was accepted as idiopathic acquired angioedema.⁴ If idiopathic acquired angioedema improved in response to antihistamines, it was defined as IH-AAE.⁴ Recurrent IH-AAE was defined when three or more episodes of angioedema had occurred within the past 12 months.¹³

Detection of either anti-thyroid peroxisomal antibody (anti-TPO) (normal range, 0–57 U/mL) and/or anti-thyroglobulin antibody (anti-T) (normal range, 0–64 U/mL) in serum above normal ranges was considered TA. The presence of thyroid autoantibody in addition to thyroid dysfunction and/or ultrasonographic (USG) abnormalities was considered autoimmune thyroid disease. In terms of autoimmune thyroid disease, the patients were assessed by using thyroid USG for criteria such as gland echogenicity, USG texture, volume, and pseudonodular hypoechoic infiltration.^{14,15}

The diagnosis of hypothyroidism was established by clinical and laboratory criteria of free thyroxine (FT₄) of <0.7 ng/dL, thyroid-stimulating hormone (TSH) of >4.94 μ IU/mL. The patients were classified as having subclinical hypothyroidism if they were clinically euthyroid with a normal FT₄ level but elevated TSH levels. The diagnosis of hyperthyroidism was based on the detection of low-serum TSH values (<0.35 μ IU/mL) and elevated levels of FT₄ (>1.48 ng/dL) in serum.

Investigations

The diagnosis of recurrent IH-AAE was made according to the algorithm given in Fig. 1. Anti-TPO, anti-T, FT₄, and TSH were measured in all patients

with recurrent IH-AAE and in the healthy control group. Those with positive thyroid autoantibodies and/or impaired thyroid function underwent thyroid USG.

Management and Follow-up

All the patients diagnosed with recurrent IH-AAE were followed up at our clinic at 3-month intervals. Prophylaxis with an antihistamine (oral desloratadine 2.5 mg for children < 6 years of age and 5 mg for children $\geq$ 6 years of age per day) was started for patients with frequently recurrent IH-AAE ($\geq$ 2 episodes in the past 3 months) on admission. If angioedema did not recur within 3 months of treatment, then the patient was defined as responsive to treatment and the prophylaxis was stopped. Patients with TA and/or thyroid dysfunction in both groups were also evaluated in the Pediatric Endocrinology Clinic. These patients were regularly followed up and investigated by the pediatric endocrinologist (A.B.) with additional thyroid autoantibody measurements, thyroid function tests, thyroid USG, thyroid scintigraphy and/or thyroid biopsy when indicated. The pediatric endocrinologists treated the children diagnosed with thyroid autoimmune diseases who were observed in the follow-up to have hypo- or hyperthyroidism.

Statistical Analysis

The Statistical Package for Social Sciences 15.0 software (SPSS, Inc., Chicago, IL) was used to perform the statistical analysis. A descriptive analysis was used to determine the characterization of the patients. Descriptive statistics were expressed as frequencies and percentages for categorical variables, whereas quantitative data were expressed as mean (standard deviation) for normally distributed variables and as medians (minimum-maximum) for non-normally distributed data. Group comparisons were established by using the Mann-Whitney *U*-tests for medians and the Student's *t*-test for means (standard deviations). The Pearson χ^2 test and/or Fisher exact test were used to compare categorical variables between the groups. A two-sided value of $p < 0.05$ was considered statistically significant.

RESULTS

Eighty consecutive children with recurrent IH-AAE (49 boys [61.3%]) were enrolled in the study group. Demographic and clinical characteristics of the children with recurrent IH-AAE are presented in Table 1. Thirty-nine of the 80 healthy children (48.8%) in the control group were boys, and the median age was 8 years (range, 20 months to 17.6 years). The two groups were well matched in terms of age and sex ($p > 0.05$).

Table 1 Demographic and clinical characteristics of children with recurrent IH-AAE ($n = 80$)

Age, median (min-max), y	8.3 (1.1–17)
Girls, no. (%)	31 (38.8)
No. angioedema episodes within the past 12 mo, median (min-max)	3 (3–12)
Atopy, no. (%)	31 (50.8)
Localization of angioedema, no. (%)	
Face	78 (97.5)
Extremity	19 (23.8)
Personal history of comorbid atopic diseases, no. (%)	29 (36.3)
Allergic rhinitis	26 (32.5)
Asthma	5 (6)
Atopic eczema	9 (11.3)
Family history of atopic diseases, no. (%)	34 (43.6)

Min-max = minimum-maximum.

TA was shown in 11 patients (13.7%) in the recurrent IH-AAE group. Anti-TPO was present in 10 patients in this group, whereas only one patient revealed anti-T positivity. All the patients were euthyroid, but three of the patients who were anti-TPO antibody positive were diagnosed with Hashimoto thyroiditis according to their thyroid USG (3.7%). The clinical and laboratory characteristics of these patients are given in Table 2.

In the control group, TA was observed in two patients (2.5%) who had only anti-T positivity (99.3 IU/mL and 60.3 IU/mL, respectively). These two patients had normal thyroid function tests and thyroid USG findings, and, therefore, no autoimmune thyroid disease was detected in the control group. The two groups were significantly different with respect to TA, which was higher in the recurrent IH-AAE group versus the control group (13.7% versus 2.5%; $p = 0.009$) but similar with respect to autoimmune thyroid disease (3.7% versus 0%; $p = 0.2$).

The median follow-up of the recurrent IH-AAE group was 34 months (range, 12–45 months). All of the patients are still euthyroid, and no new cases of Hashimoto thyroiditis were detected. Patients with recurrent IH-AAE with and without TA were not different with respect to either the need or the duration of antihistamine prophylaxis ($p > 0.05$ for both).

DISCUSSION

This is a case-control study that was conducted to assess the association between TA and/or autoimmune thyroid disease and recurrent IH-AAE in children. It was demonstrated that TA but not thyroid autoimmune disease is apparently more frequent in children with recurrent IH-AAE. There is no study with which to make a head-to-head comparison of our

Table 2 Characteristics of 11 patients with TA and recurrent IH-AAE

Patient No.	Age (y)/Sex	Angioedema Episodes Within the Past Year	FT ₄ , ng/dL (normal range, 0.7–1.48 ng/dL*)	TSH, μ IU/mL (normal range, 0.35–4.94 μ IU/mL*)	Anti-TPO, IU/mL (normal range, 0–57 IU/mL*)	Anti-T, IU/mL (normal range, 0–64 IU/mL*)	Thyroid USG
1	9/F	3	1.22	3.51	88.5	33	N
2	6/F	3	3.8	1.41	77	46.5	N
3	4.5/M	3	1.24	3.81	46.1	74	N
4	15/F	3	1.03	1.7	60.8	48.4	N
5	4/M	3	1.17	2.50	60	52.4	N
6	4.5/M	3	1.6	3.4	71.1	38.2	N
7	16/F	4	1.18	2.40	122.1	47.4	N
8	13/F	3	1.04	0.30	108	40.4	Thyroiditis
9	5/M	3	1.42	4.32	72.3	37.5	N
10	9/F	8	0.92	4.83	69.6	44.9	Thyroiditis
11	15/F	4	1.21	1.48	108.2	11.8	Thyroiditis

AntiT = antithyroglobulin antibody; AntiTPO = antithyroid peroxidase antibody; F = female; FT₄ = free thyroxine; M = male; N = normal; TSH = thyroid-stimulating hormone; USG = ultrasonography.

*Normal test values in our laboratory.

data. Previous published reports about the relationship between allergic diseases and TA and/or autoimmune thyroid diseases primarily focused on patients with CU.^{7,8,16,17} In these studies, 35–67.3% of patients with CU were also reported to have associated angioedema.^{8,12} In some of these studies, 3.3–4.3% of patients with CU were reported to first present with angioedema alone.^{7,8} However, these studies did not provide the details of the relationship between angioedema and TA; their report was only confined to demographic data.

A considerably low rate of TA comorbid with CU has been reported in children (4%) compared with adults (12–57%).^{7,18,19} In this respect, the presence of TA in children with recurrent IH-AAE in our study (13.7%) is higher than that reported in children with CU. However, in two adult studies, *viz.* the studies of Leznoff *et al.*⁷ and Turktaş *et al.*,⁸ all the patients with CU who were shown to have TA were reported to have angioedema. In addition, the frequencies of association were very similar to ours: 12.1% in the study by Leznoff *et al.*⁷ and 11.7% in the study by Turktaş *et al.*,⁸ respectively. Another recent case-control study in adults showed that, in cases of TA comorbid with CU, the risk of angioedema increases 16-fold.²⁰ Thus, we think that the presence of angioedema, whether as recurrent isolated angioedema or as comorbid with CU, has more of an association with TA compared with isolated CU. However, there are also CU studies that have been conducted in children that do not support our data.^{16,21} In these pediatric studies without control groups, the rate of angioedema that accompanies CU was reported as between 42% and 59%; TA, however, was found to be between 0% and 3.7%.^{21,22} We believe that the difference between previous pediatric studies and ours in terms of TA results may be related to the inclusion of children with recurrent angioedema without urticaria.

It is also known that urticaria has a more-severe and prolonged course in adult patients who have TA and/or autoimmune thyroid disease.^{8,11,17} A positive autologous serum skin test (ASST) result, which can be assessed as an indirect indicator of autoimmunity, was found to be associated with CU in adults, and this was assessed as a poor prognostic factor with a positive thyroid autoantibody.¹⁷ However, data on this issue are limited in children, and neither comorbid angioedema nor positive ASST result or thyroid pathology was found to be related to the CU prognosis.^{21,22} Although we did not investigate ASST in our patients, the duration of treatment with antihistamine did not make a difference among our patients with respect to TA positivity. Certainly, questions about prognosis always need long-term follow-ups. In a study by Confino-Cohen *et al.*,¹⁰ which is the longest follow-up study in adult patients with CU, autoimmune diseases such as autoimmune thyroid (odds ratio [OR]: 17.3), type 1

diabetes (OR:7.7), and rheumatoid arthritis (OR:13.2) were found to occur more in patients with CU when compared with the control group during a follow-up time of 10 years. However, only 3.6% of patients with CU were shown to have hypothyroid autoimmune disease in the first 6 months of the same study.¹⁰

There were limitations in our study. One of these was the duration of the follow-up. Long-term follow-ups are important in assessing the natural course of TA in the development of autoimmune thyroid diseases or other autoimmune diseases. We did not assess other serologic autoantibodies, such as the antinuclear antibody, rheumatoid factor, or celiac antibodies, which is another limitation. Also, although the case-control design of the study was appropriate in investigating an association between two diseases or conditions, the number of patients and controls in our study was too limited to generalize our results to the population. Yet again, as far as we know, our study is the only one to have investigated an association between recurrent angioedema and TA and/or autoimmune thyroid diseases in children, a contribution that may be regarded as a preliminary effort for future population studies.

In conclusion, recurrent IH-AAE may be related or associated with TA and/or autoimmune thyroid diseases in some children. Our study does not answer the question as to whether the association between recurrent angioedema and TA and/or autoimmune thyroid diseases is a causal link or only an epiphenomenon (no causal link between the two), a matter that may deserve further investigation with respect to the pathogenesis.

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