

Chronic urticaria: association with thyroid autoimmunity

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Background: Though autoimmune phenomena have been regularly associated with chronic urticaria in adults, data in children are sparse.

Aim: To describe our experience with children and adolescents with chronic urticaria and autoimmunity.

Methods and Results: Of 187 patients referred for evaluation of chronic urticaria during a 7.5 year period, eight (4.3%), all females aged 7–17 years, had increased levels of antithyroid antibody, either antithyroid peroxidase antibody (n = 4, >75 IU/ml), antithyroglobulin antibody (n = 2, >150 IU/ml), or both (n = 2). The duration of urticaria was four months to seven years. Five patients were euthyroid, one of whom was found to have increased antithyroid antibody levels five years after onset of the urticaria. One patient was diagnosed with Hashimoto thyroiditis three years before the urticaria, and was receiving treatment with thyroxine. Two other hypothyroid patients were diagnosed during the initial work up for urticaria (thyroxine 9.2 pmol/l, thyroid stimulating hormone (TSH) 40.2 mIU/l) and five years after onset of the urticaria (thyroxine 14 pmol/l, TSH 10.3 mIU/l). Both were treated with thyroxine but neither had remission of the urticaria. Five patients had a low positive titre of antinuclear antibodies.

Conclusion: Children with chronic urticaria should be screened periodically for thyroxine, TSH, and antithyroid antibodies, as thyroid autoimmunity and hypothyroidism may appear several years after onset of the urticaria.

Childhood chronic urticaria is a common disorder characterised by the appearance of hives on a continuous or frequently recurrent basis for more than six weeks.^{1,2} In most cases the aetiology is unknown, but in some cases the causative factors are identified and include mainly infections or physical stimuli.^{1–4} Autoimmune thyroid disease has been associated with chronic urticaria in adults but rarely in children,^{2,5–8} and autoimmune mast cell disease, mentioned in some adults series,^{9,10} has not been described in children. Recently, case reports of children with chronic urticaria associated with coeliac disease, type 1 diabetes, juvenile rheumatoid arthritis (JRA), and familial occurrence of autoimmune diseases have been published.^{11,12}

We describe our experience with children and adolescents with chronic urticaria and associated autoimmunity.

PATIENTS AND METHODS

From January 1994 to June 2001, 187 children and adolescents (age range 6–18 years; male:female ratio 0.92) were referred to the allergy clinic for evaluation of chronic urticaria (≥ 6 weeks duration). Each patient underwent complete clinical history and physical examination. The work up for chronic urticaria included the following: (1) blood tests for complete blood count, sedimentation rate, blood chemistry, hepatitis B surface antigen, antibody titres for hepatitis B virus, herpes simplex virus, Epstein-Barr virus, cytomegalovirus and mycoplasma, antistreptolysin antibody, antinuclear antibody (ANA) and anti-DNA antibody if needed, levels of serum complement components C3 and C4, free thyroxine (normal range 10.5–25.7 pmol/l), thyroid stimulating hormone (TSH) (normal range 0.4–4 mIU/l), antithyroid peroxidase (anti-TPO) antibodies (normal <75 IU/ml), antithyroglobulin antibodies (normal <150 IU/ml), and anti-islet cell antibodies in patients with a family history of type 1 diabetes; (2) urine analysis and culture, nasal and throat swabs; (3) chest and sinus x rays; (4) prick skin tests with food allergens; and (5) ice cube test for cold induced urticaria and skin stroking for dermatographism. Follow up of the patients included

periodic visits and blood tests for free thyroxine, TSH, and antithyroid antibodies. The antithyroid antibody levels were measured using immunometric enzyme immunoassay (Or-gentec Diagnostika GmbH, Mainz, Germany). Thyroxine and TSH levels were measured by a solid phase competitive analogue sequential chemiluminescent immunoassay (Im-mulite 2000, DPC, Los Angeles, CA).

All patients were treated with H₁ receptor blocking medication (loratadine, cetirizine). Short courses of oral corticosteroids were reserved for severe exacerbations.

RESULTS

Only eight of the 187 patients evaluated had increased levels of antithyroid antibodies, and these constituted the study sample. The results of their work ups for food allergy or physical or infectious causes were negative. Tables 1 and 2 present the pertinent patient data.

In four patients (nos 1, 2, 4, 6), family history was positive for autoimmune and endocrinological diseases (juvenile rheumatoid arthritis, type 1 diabetes, Hashimoto thyroiditis, and hypothyroidism). Patient 1 was found to have Hashimoto thyroiditis during the work up for chronic urticaria, and treatment with thyroxine (100 µg/day) was started immediately. In patient 6, a diagnosis of Hashimoto thyroiditis had been made three years prior to onset of the chronic urticaria; she was being treated with thyroxine 100 µg daily. Her pretreatment thyroxine and TSH levels were 9.3 pmol/l and 1.4 mIU/ml, respectively (data not shown). Treatment with thyroxine was initiated mainly because of findings of nodular goitre.

Patients 4 and 5, both with chronic urticaria of six and seven years duration, respectively, had increased levels of antithyroid antibodies five years after onset of the urticaria.

Abbreviations: ANA, antinuclear antibody; GAD, glutamic acid decarboxylase; JRA, juvenile rheumatoid arthritis; TPO, thyroid peroxidase; TSH, thyroid stimulating hormone

Table 1 Clinical features of eight girls with chronic urticaria and positive thyroid autoantibodies taken from a cohort of 187 children and adolescents with chronic urticaria

Patient no.	Sex/age at presentation (y)	Duration of urticaria	Family history
1	F/10	9 mth	JRA (sister)
2	F/15	4 mth	Hypothyroidism (father)
3	F/17	5 mth	
4	F/13.5	6 y	Type 1 diabetes (brother)
5	F/7	7 y	
6	F/11	3 y	Hashimoto thyroiditis (mother)
7	F/8	6 mth	
8	F/11	2 y	

Table 2 Laboratory test results from eight girls with chronic urticaria and thyroid autoimmunity, taken from a cohort of 187 patients

Patient no.	TSH (mIU/l)	Thyroxine (pmol/l)	Anti-TPO (IU/ml)	Anti-Tg (IU/ml)	ANA	Anti-DNA	C3 (mg/dl)
1*	40.2	9.2	132.9	35.7	Negative	ND	ND
2	3.07	12.2	105	14	Negative	ND	113
3	1.25	13.6	26	296	Negative	ND	125
4†	0.90	17	245	133	1:160	16%	72
5‡	10.3	14	870	1605	1:80	10%	87
6§	0.85	15.7	1076	56	1:40	ND	106
7	2	20	248	599	1:40	ND	116
8	3.2	15.4	70	333	1:160	12%	143
Normal range	0.4–4	10.5–25.7	<75	<150		<20%	125±25

Tg, thyroglobulin; ND, not done.

*Increased levels of antithyroid antibodies and TSH detected during the initial work up.

†Increased levels of antithyroid antibodies detected five years after onset of urticaria; this patient also had increased levels of anti-GAD antibodies.

‡Increased levels of antithyroid antibodies and TSH detected five years after onset of urticaria.

§Hashimoto thyroiditis diagnosed three years prior to chronic urticaria. On thyroxine treatment at evaluation.

Patient 5 also had an increased TSH level, and she was prescribed thyroxine. Patient 4 had a family history (brother) of type 1 diabetes and increased levels of antihydroxyglutamic acid decarboxylase (GAD) antibodies (55.2 units, normal <6.5), no evidence of insulin autoantibodies and islet cell antibodies, and a normal oral glucose tolerance test. Five patients had positive low ANA titres (1/40–1/160), with negative findings for anti-DNA antibodies in the three patients who were tested. C3 levels were mildly reduced in two patients.

None of the three patients treated with thyroxine had a remission of the urticaria.

None of the other 179 patients with chronic urticaria was hypothyroid or had a positive test for ANA.

DISCUSSION

Most cases of chronic urticaria in children are idiopathic. Physical stimuli, infections, and stress comprise the majority of identified causative factors.^{1–4}

The association of chronic urticaria with autoimmune thyroid disease has frequently been reported in adults. The prevalence in adult series ranges from 14% to 33%.^{5–7}

The prevalence of thyroid autoimmunity in our study was 4.3%, much lower than that in adult series of chronic urticaria, but higher than the prevalence reported to date for age matched children: in two population based studies of the 10–11 to 18 year age group, Rallison and colleagues¹³ reported a 1.27% prevalence of autoimmune thyroiditis in 4819 children, and Marwaha and colleagues¹⁴ found a prevalence of 1.6% in 6283 girls. Jaksic and colleagues¹⁵ found a prevalence of 0.35% in 5462 school age children.

Although 90 of our entire group of 187 children and adolescents with chronic urticaria were males, all the patients with chronic urticaria and thyroid autoimmunity were females.

This is in accordance with findings of a higher prevalence of thyroid autoimmunity in women in cross sectional studies.¹⁶ Other investigators also showed that the association of chronic urticaria with thyroid autoimmunity is more common in females.¹⁷

Our literature review yielded no large series of thyroid autoimmunity in chronic urticaria in children, although several case reports have been published. Dreyfus and colleagues⁸ described a 9 year old boy with chronic urticaria and antithyroid microsomal antibodies who had prolonged remission with thyroxine treatment. Levine and colleagues¹¹ reported an 11 year old girl who had chronic urticaria with antithyroid antibodies, who was also found to have coeliac disease. Her family history revealed chronic urticaria and thyroid autoimmunity in three generations on the maternal side. In another report of two children, aged 15 and 13 years, with chronic urticaria, one child also had type 1 diabetes, increased levels of antithyroglobulin antibodies, and low titre of ANA; the other later developed systemic type juvenile rheumatoid arthritis. He also had a positive family history of autoimmune disorders, such as thyroid disease, type 1 diabetes, and coeliac disease.¹²

Similar to the patients reported by Levine and colleagues¹¹ and Dalal and colleagues,¹² four of our patients had a positive family history of autoimmune diseases, and five had positive titres of ANA, with low C3 levels in two. However, none, except patient 4, had any clinical or laboratory evidence of autoimmune disease other than the thyroid autoimmunity. Patient 4, whose brother had type 1 diabetes, also had increased levels of anti-GAD antibodies, but repeated oral glucose tolerance tests during the subsequent two years of follow up were consistently normal. It is known that type 1 diabetes may coexist with other endocrine diseases and that organ

specific antibodies are a frequent occurrence in these patients.¹⁸ Jaeger and colleagues¹⁹ found that type 1 diabetes associated antibodies and antithyroid antibodies were significantly more frequent in first degree relatives of patient with type 1 diabetes than in healthy controls.

Three of our patients (nos 1, 5, 6) were hypothyroid. Patient 1 was diagnosed during the work up for chronic urticaria; patient 6, three years prior to the appearance of the urticaria; and patient 5, five years after the appearance of the urticaria. In one additional patient (no. 4), antithyroid antibodies were detected only five years after the appearance of the urticaria. These findings may indicate that the thyroid autoimmunity in chronic urticaria is an evolving process and may be manifested before, concomitant with, or several years after the appearance of the urticaria. They may also explain the low prevalence of thyroid autoimmunity in our series compared to adults: adolescent patients with chronic urticaria may be diagnosed with thyroid autoimmunity only as young adults.

The mechanism whereby thyroid autoimmunity is associated with urticaria is poorly understood. The antithyroid IgG antibodies may not be directly involved in the mast cell degranulation and pathogenesis of the chronic urticaria, but only serve as indicators of autoimmunity.⁶ Skin biopsy specimens from patients with chronic urticaria, with or without Hashimoto thyroiditis, were indistinguishable by light microscopy, and no immune complex deposition was observed.²⁰ Several researchers have observed serum histamine releasing activity in a subgroup of adult patients with chronic urticaria which was attributable to an IgG autoantibody directed against the alpha chain of the high affinity IgE receptor (FcεRIα) of the mast cells or, less commonly, against IgE itself.^{9,10} In addition, clustering of thyroid antimicrosomal antibodies was found in patients with a positive autologous serum test, indicating the presence of functional histamine releasing autoantibodies.²¹ In a series of patients with chronic urticaria only patients with chronic urticaria and Hashimoto thyroiditis had anti-Fcε RI antibodies in their sera that could induce degranulation of normal basophils.²⁰ These antibodies have not been investigated systematically in children with chronic urticaria. Greaves¹ found that three of seven tested patients aged 13–16 years had functional anti-FcεRI antibodies.

None of the three hypothyroid patients treated with thyroxine had a remission of the urticaria, in contrast to the 9 year old euthyroid patient reported by Dreyfus and colleagues,⁸ and the euthyroid and hypothyroid patients in the series of Rumbryt and colleagues²² and Gaig and colleagues.¹⁷ Moreover, patient 6 developed urticaria while on treatment with thyroxine (table 2). Although we have treated only hypothyroid children, our experience does not support the use of thyroxine treatment in euthyroid patients with chronic urticaria.

Euthyroid patients with a positive anti-TPO antibody, have an appreciable risk of progression to hypothyroidism.¹⁶ Annual reassessment of thyroid function in patients with chronic urticaria and increased antithyroid titres is recommended.²³ However, our experience shows that the thyroid autoimmunity may appear several years after the onset of chronic urticaria, emphasising the importance of follow up and periodic blood tests for thyroxine/TSH and antithyroid antibodies in children with chronic urticaria. Whether children and adolescents with chronic urticaria and thyroid autoimmunity belong to the subgroup of chronic urticaria patients with autoimmune mast cell disease is still to be determined.

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REFERENCES

- 1 **Greaves MW**. Chronic urticaria in childhood. *Allergy* 2000;**55**:309–20.
- 2 **Joint Task Force on Practice Parameters**. The diagnosis and management of urticaria: a practice parameter. Part I: Acute urticaria/angioedema. Part II: Chronic urticaria/angioedema. *Ann Allergy Asthma Immunol* 2000;**85**:521–44.
- 3 **Harris A**, Twarog FJ, Geha RS. Chronic urticaria in childhood: natural course and etiology. *Ann Allergy* 1983;**51**:161–5.
- 4 **Volomakis M**, Katsarou-Katsanri A, Stratigos J. Etiologic factors in childhood chronic urticaria. *Ann Allergy* 1992;**69**:61–5.
- 5 **Lauter CB**, Ospina L, Aslani K. Chronic idiopathic urticaria and thyroid autoimmunity: a second opinion [abstract]. *J Allergy Clin Immunol* 2001;**107**:S51.
- 6 **Heymann WR**. Chronic urticaria and angioedema associated with thyroid autoimmunity. Review and therapeutic implications. *J Am Acad Dermatol* 1999;**40**:229–32.
- 7 **Zauli D**, Deleonardi G, Foderaro S, et al. Thyroid autoimmunity in chronic urticaria. *Allergy Asthma Proc* 2001;**22**:93–5.
- 8 **Dreyfus DH**, Schocket AL, Milgrom H. Steroid-resistant chronic urticaria associated with anti-thyroid microsomal antibodies in a nine-year-old boy. *J Pediatr* 1996;**57**:6–8.
- 9 **Hide M**, Francis DM, Grattan CEH, Hakimi F, Greaves MW. Autoantibodies against the high-affinity IgE receptor as a cause for histamine release in chronic urticaria. *N Engl J Med* 1993;**328**:1599–604.
- 10 **Tong LJ**, Balakrishnan G, Kochan JP, et al. Assessment of autoimmunity in patients with chronic urticaria. *J Allergy Clin Immunol* 1997;**99**:461–5.
- 11 **Levine A**, Dalal I, Bujanover Y. Celiac disease associated with familial chronic urticaria and thyroid autoimmunity in a child. *Pediatrics* 1999;**104**:e25.
- 12 **Dalal I**, Levine A, Somekh E, et al. Chronic urticaria in children: expanding the "autoimmune kaleidoscope". *Pediatrics* 2000;**106**:1139–41.
- 13 **Rallison ML**, Dobyms BM, Meikle AM, et al. Natural history of thyroid abnormalities: prevalence, incidence and regression of thyroid diseases in adolescents and young adults. *Am J Med* 1991;**91**:363–70.
- 14 **Marwaha RK**, Tandon N, Karak AK, et al. Hashimoto's thyroiditis: countrywide screening of goitrous healthy young girls in post-iodization phase in India. *J Clin Endocrinol Metab* 2000;**85**:3748–802.
- 15 **Jaksic J**, Dumic M, Filipovic B, et al. Thyroid diseases in a school population with thyromegaly. *Arch Dis Child* 1994;**70**:103–6.
- 16 **Saravanan P**, Dayan CM. Thyroid autoantibodies. *Endocrinol Metab Clin N Am* 2001;**30**:315–37.
- 17 **Gaig P**, Garcia-Ortega P, Enrique E, et al. Successful treatment of chronic idiopathic urticaria associated with thyroid autoimmunity. *J Invest Allergol Clin Immunol* 2000;**10**:342–5.
- 18 **Rattarasarn C**, Diosdado MA, Ortego J, et al. Thyroid autoantibodies in Thai type I diabetic patients: clinical significance and their relationship with glutamic acid decarboxylase antibodies. *Diabetes Res Clin Pract* 2000;**49**:107–11.
- 19 **Jaeger C**, Hatzigelaki E, Petzoldt R, et al. Comparative analysis of organ-specific autoantibodies and celiac-disease associated antibodies in type I diabetic patients, their first-degree relatives, and healthy control subjects. *Diabetes Care* 2001;**24**:27–32.
- 20 **Kandeel AA**, Zeid M, Helm T, et al. Evaluation of chronic urticaria in patients with Hashimoto's thyroiditis. *J Clin Immunol* 2001;**21**:335–47.
- 21 **Saboe RA**, Greaves MW. The pathogenesis of chronic idiopathic urticaria. *Arch Dermatol* 1997;**133**:1003–8.
- 22 **Rumbryt MD**, Kats JL, Schocket AL. Resolution of chronic urticaria in patients with thyroid autoimmunity. *J Allergy Clin Immunol* 1995;**96**:901–5.
- 23 **Kaplan AP**. Chronic urticaria and angioedema. *N Engl J Med* 2002;**346**:175–9.