

Idiopathic (autoimmune) chronic urticaria

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ABSTRACT

A case of idiopathic chronic urticaria (CU) is described briefly. The clinical characteristics, pathogenesis, diagnosis, and management of this disease are discussed followed by clinical pearls and pitfalls for the practicing allergist as well as the immunologist. CU, defined as recurring attacks of hives lasting for >6 weeks, is a common disorder for which the cause is determined in <20% of patients. Although the pathogenesis of idiopathic CU is not certain, the immune dysregulation/disruption causing autoimmunity is blamed. The diagnosis is based principally on the patient's history. Autologous serum skin test possibly should be performed in older children as a screening test for idiopathic autoimmune CU. This test shows the availability of serum IgG autoantibodies directed against the α -chain of Fc ϵ RI. However, basophil mediator release assay still is accepted as a gold standard. Treatment is aimed first at avoiding underlying causative factors. Medications varying from H₁-antihistamines to plasmapheresis as well as immunosuppressive therapies should be considered depending on clinical improvement. Spontaneous resolution of the disease is probable also.

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Question

A 15-year-old boy presented with a 10-month history of severe urticaria and angioedema. Urticarial hives lasted for <24 hours and left no residual purpura. Hives occurred daily with a predilection for pressure areas. There was no history of insect bite, vaccination, or medication use. Angioedema occurred daily with facial and throat swelling. An autologous serum skin test (ASST) was positive. There was no dermatographism. CBC, C-reactive protein, and sedimentation rate were normal. The following investigations were negative or normal: complete metabolic profile; immunoglobulins; antinuclear antibody; extractable nuclear antigen; organ-specific autoantibodies; C3, C4, and C1 esterase inhibitor; Coomb's test; and thyroid function tests. An infection screen with the following tests was negative: serology for hepatitis A/B/C, toxoplasmosis and antistreptolysin antibodies, a Mantoux test, and chest x ray. Cytomegalovirus and Epstein-Barr virus IgG antibodies indicated past infection, but *Helicobacter pylori*-specific IgG antibody was negative. Treatment with H₁/H₂-antihistamines, prednisolone, and cyclo-

sporin was unsuccessful. There was a marked improvement after 1 week with methotrexate, and within 2 months the patient was symptom free, and 2% ephedrine spray was needed for the angioedema. Which of the following statements are correct?

- A. ASST is the gold standard for diagnosing idiopathic chronic urticaria (ICU).
- B. The frequency of atopy in ICU patients is higher and the serum immunoglobulin E (IgE) usually is elevated.
- C. Functional histamine-releasing anti-Fc ϵ RI autoantibodies can be detected with basophil mediator release assay.
- D. Immunoreactive but nonfunctional anti-Fc ϵ RI autoantibodies were detected in other autoimmune diseases, e.g., dermatomyositis and pemphigus.
- E. Molecular mimicry between human thyroid peroxidase and peroxidase of *H. pylori* CagA-positive strains might be a possible trigger in the development of autoimmune thyroid disease as well as idiopathic autoimmune CU (IACU).

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Chronic urticaria is a common disabling disorder occurring in 0.1% of the population, with an average duration of 3–5 years in adults. CU, defined as recurring attacks of hives lasting for >6 weeks, is a common disorder for which the cause is determined in <20% of patients. However, the information regarding CU in childhood is limited to a few reports.¹ Most cases in children are idiopathic and causal factors were iden-

Table 1 Skin disorders resembling ICU

Skin Disorders	Presentation
Allergic contact dermatitis	Mostly facial
Dermatomyositis	Mostly facial
Recurrent erythema multiforme	Mainly affects limbs and face
Polymorphous light eruption	Mostly facial
Fixed drug eruption	Mucocutaneous
Urticarial vasculitis	Mostly limbs

tified in ~20% of patients including physical factors, stress, and aeroallergens.

ICU is one of the enigmas of allergy and dermatology. In the past 10 years, two possibilities have been proposed to explain its mechanisms: *H. pylori* and the autoimmune origin. *H. pylori* infections of the stomach/duodenum are frequently implicated as a causative agent, but some reports do not confirm this association. Autoimmunity may play a role in CU, at least for a subpopulation of patients.

At least one-third, ranging from 25 to 60%, of ICU patients has circulating functional autoantibodies against the high-affinity IgE receptor FcεRI, or less commonly, IgE itself, causing a positive ASST.² These functional (*i.e.*, histamine-releasing) anti-FcεRIα autoantibodies are shown only in IACU and not in healthy or eczema, psoriasis, and physical urticaria. In a minority of ICU patients that lack such antibodies, an unknown serum factor, *e.g.*, non-IgG reactant(s) or so-called endogenous histamine-releasing factor, is blamed. However, the association between autoimmunity and ICU is reported rarely in children.³ The association of ICU with various types of autoimmune diseases, *e.g.*, celiac and diabetes mellitus, is well-known in adults. Furthermore, the prevalence of autoimmune thyroid disease is higher in adults (14–33%) than in children (0.35–4.3%).

CLINICAL CHARACTERISTICS

The cardinal feature is the repeated occurrence of short-lived cutaneous wheals accompanied by rash and itching. Individual wheals last <24 hours and may be round or irregular. They may occur anywhere on the skin, including the scalp and palms (Table 1). The itch is almost habitual and usually worse during the nighttime and is relieved by rubbing the skin rather than by scratching.

At least one-half of the adult patients with ICU also have angioedema. However, this is rare in childhood. The swellings of angioedema last <24 hours and they are red or skin colored. Itching is less consistently associated with angioedema than with urticaria. Al-

though IACU exhibits no distinctive clinical features, all subjects who were ASST⁺ presented more severe clinical features than ASST⁻ subjects.⁴ Intercurrent febrile infections almost invariably cause nonspecific flare-ups of ICU, and parents should be warned about this.

PATHOGENESIS

The first hypothesis is that the immune dysregulation caused by the antigen in a specific disease may secondarily affect other organs. For instance, the cross-reactivity between CagA plus *H. pylori* strains and thyroid peroxidase may trigger autoimmune thyroiditis.⁵

A second possibility is that a general immune disruption makes CIU another marker of autoimmunity. This concept also is supported by (a) the association with a variety of autoimmune diseases, anti-IgE antibodies, and ASST⁺; (b) availability of IACU patients who are not responsive to antihistamines or are dependent on oral steroids and/or immunosuppressant; and (c) the association with human leukocyte antigen DR4 and DQ8 in some patients.⁶

DIAGNOSIS

An extensive workup usually is not indicated or helpful in identifying a cause. The diagnosis is based on the patient's history and it is vital to spend time documenting this in detail (Table 2).

ASST possibly should be performed in older children as a screening test. The gold standard, basophil mediator release assay, is necessary to confirm the presence of functional anti-FcεRI or anti-IgE autoantibodies or other histamine releasing factors. Basophil CD63 and CD203c marker expressions indicating mediator release in flow cytometry can be studied also.⁷ Immunosorbent and immunobinding assays are unacceptable for diagnosis of IACU and the functional assay is required.

CBC, biochemistry, complements levels, and skin tests are noncontributory. However, basopenia is a regular feature of CIU and IACU. Eosinophilia should prompt a search for parasite infestation. Total IgE, autoimmune markers, antithyroid autoantibodies, *H. Pylori*-specific IgG antibodies, and placebo-controlled oral food challenge as well as skin biopsy are worthy of consideration.

MANAGEMENT

Treatment is aimed first at avoiding underlying causative or exacerbating factors. Common-sense measures are helpful, including avoidance of tight and woollen underclothes. Aspirin and NSAIDs should be avoided. After removal of specific and nonspecific triggers, the

Table 2 Significance of diagnostic procedures in ICU

Procedures	Importance
Patient's medical history	Essential
Functional tests	
Basophil mediator release assay	Gold standard test
Flow cytometric evaluation of basophil CD63 and CD203c marker expressions	Still experimental and not commonly used, but promising
ASST	Screening test
Nonfunctional tests	
Immunosorbent and immunobinding assays, <i>e.g.</i> , ELISA and Western blot	Unacceptable
Others	
Total IgE, autoimmune markers, <i>e.g.</i> , ANA, antithyroid autoantibodies, specific IgG antibodies, gastroscopy, and urease testing for <i>H. Pylori</i>	Contributory
Placebo-controlled oral food challenge and skin biopsy	Contributory
CBC, biochemistry, and complements levels	Noncontributory
Skin tests	Noncontributory

ANA = antinuclear antibody.

use of symptomatic medications generally attenuating the mediator effects should be considered.

H₁-receptor antagonists remain the mainstay of treatment. The newer low-sedating antihistamines desloratadine, fexofenadine, and levocetirizine are tried first. Sedating antihistamines are useful if symptoms are causing sleep disturbance. Low-dose doxepin is especially suitable for patients with associated depression. There is controversy as to whether the addition of an H₂-receptor antagonist or a leukotriene antagonist is helpful. Second-line agents include cyclosporine, short courses of oral corticosteroids, i.v. immunoglobulins, and plasmapheresis. If a patient with IACU proves unresponsive to H₁-antihistamines, then the additional immunosuppressive options may be warranted such as methotrexate,⁸ stanazol, rofecoxib, cyclophosphamide, and photoglyph(chemo)therapy. Administration of a 2% aqueous ephedrine spray is safe and effective for angioedema attacks.

Answers to the Questions

- Wrong.
- Both statements are wrong.
- Correct.
- Correct.
- Probably correct.

Pearls

- Children have the same ability as adults to produce functionally active autoantibodies directed against IgE or IgE receptor; and IACU occurs in children in as many as 30% of cases.¹

- The ASST is the screening test; basophil mediator release assay is the gold standard and functional test.
- Although there are no significant clinical differences between autoimmune and nonautoimmune ICU; IACU patients have more severe clinical features and are resistant to treatment.
- Most frequently documented infectious agents in CU are *Escherichia coli*, A group β -hemolytic streptococcus, and *H. pylori*.
- Improvement in IACU may be seen with L-thyroxine, diet, and the eradication of *H. Pylori*.
- Food-additive-induced urticaria is not a substantiated cause of ICU.⁹

Pitfalls

- ICU may exacerbate with progesterone therapy.
- ICU is commonly confused with some skin disorders, *e.g.*, contact allergic dermatitis, and fixed drug eruption (Table 1).
- Annual reassessment of thyroid function in patients with ICU is recommended.
- Immunosorbent and immunobinding assays are unacceptable for diagnosis of IACU, and functional assays are required (Table 2).
- The syndrome of thyroid autoimmunity and ICU can be associated with a marked worsening of reactive airway disease as well as anaphylaxis.¹⁰

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