

Chronic Urticaria: Diagnosis, Management, and Future Directions

Moshe Ben-Shoshan, MD, MSc, Pediatric Allergy and Immunology Specialist

Presented at McGill University's Thursday Evening Learning Series on March 7, 2013.

Definition and classifications

Chronic urticaria (CU) is a common, debilitating condition. CU can be diagnosed when an individual presents with transient wheals that appear almost daily and last more than six weeks in duration.¹ CU is defined as spontaneous (CSU) when no inducible trigger can be identified. CSU is considered the most common type of CU.² Inducible CU is defined when a trigger for CU can be identified.³ Inducible CU includes physical urticaria (17% of CU cases).⁴ Physical urticarias are defined according to the physical trigger (e.g., as mechanical, cold, solar, heat, delayed pressure, aquagenic, and vibrative urticarias). Cholinergic urticaria is associated with an increase in core body temperature due to physical exercises and spicy food. Contact urticaria is mainly associated with an occupational contact allergen. Other inducible urticarias include urticaria related to infection (mainly parasites) or to drug hypersensitivity (nonsteroidal anti-inflammatory drugs).⁵⁻⁷ Urticaria-related diseases include: urticaria vasculitis, urticaria pigmentosa, schnitzler's syndrome and cryopirin-associated periodic fever (CAPS).²

Prevalence and natural history

The point prevalence of CSU is 0.5 to 1% for the entire population.⁸ The lifetime prevalence of CSU is 3% in adults and 0.1 to 0.3% in children.⁹ In adults, CSU is more common in women (odds ratio = 3.82), but there is no

Noah's Case

Noah is a healthy, 18-year-old teenager with mild asthma. Two years ago, he began complaining of hives almost daily. He was treated with high doses of antihistamines, antileukotriens, and anti-H₂ drugs with no improvement. He has had to take numerous days off of work due to unbearable itchiness. He was started on steroids up to 30 mg a day, which improved his condition. However, he could not stop taking steroids for even one day, because he would revert back to his former state. In addition, he was admitted for IV steroids last year due to adrenal suppression.



gender preference in children.⁹ Individual lesions and hives associated with chronic urticaria last 4 to 36 hours. Clearing of the central area may result in an annular pattern. Up to 50% of those with chronic urticaria will also have angioedema.¹⁰⁻¹¹ CSU



resolves spontaneously in only 30 to 55% of both adults and children within five years, 20% continue with the disease for more than 10 years.¹² The resolution rate in physical urticaria is reported to be lower.¹³

Pathogenesis

The pathogenesis of CSU is unclear. Given that IgE-mediated allergy rarely emerges as an aggravating factor, it is considered a chronic, inflammatory disease, rather than an allergic condition.¹⁴ About half of patients with CSU have circulating functional autoantibodies against the high affinity IgE receptor or against IgE, although it is not known why such antibodies are produced, or how the presence of such antibodies alters the course of the disease or response to treatment.¹⁵⁻¹⁶ These autoantibodies can be detected through the autologous serum skin test (*i.e.*, a skin reaction that develops after exposure to the patient's own serum) or through markers of basophil activation (*e.g.*, CD63 antigen).¹⁵ In addition, up to one third of CSU patients have high levels of autoantibodies to thyroid antigens,¹⁷ and, recently, IgE autoantibodies directed against thyroid peroxidase have been suggested to cause "autoallergic" mast cell activation, which contributes to the development of CSU.¹⁸ Although the levels of thyroid auto-antibodies is higher in CSU compared to controls, this was not associated with a higher risk for clinical thyroiditis.¹⁹

Psychological factors were thought to be a factor as well in the pathogenesis of CSU. Several reports suggest that CSU may emerge through interactions between the nervous and immune systems, and almost 50% of CSU patients present with psychosocial pathology. However, it is not yet clear whether psychosocial factors precede or follow CSU.²⁰

Diagnosis

CSU is essentially a diagnosis of exclusion in instances where no contributing factors can be

determined to be the cause of the cutaneous reaction. In almost 100% of cases of chronic urticaria, a cause is not identified. Patients should be queried on timing and onset of hives, likely triggers, recent infections, and travel history. Physical examination should include identifying and characterizing any current lesions, testing for dermatographism (hives induced by rubbing intact skin), and checking for signs of systemic illness (including recurrent fever, weight loss, and joint symptoms). An extensive work-up is not recommended for diagnosing a cause of chronic urticaria. Additional testing can be done if presentation suggests underlying disease or specific causes require confirmation (*e.g.* TSH levels, tryptase, stools for parasites, *etc.*). Guidelines recommend a complete blood count with differential and measurement of erythrocyte sedimentation rate or C-reactive protein in patients with CU.¹ When history suggests a physical urticaria, challenge testing with physical stimuli may be considered, but such testing often lacks validated challenge parameters.⁷

Treatment

A stepwise approach to treating CSU is recommended. Second-generation histamine H1-receptor antagonists are considered first-line therapy. For better symptom control, medication should be taken daily. Treatment guidelines recommend titration up to two to four times the usual dose to attain good control of hives. However, with higher doses, there is greater possibility of adverse effects, which should be discussed with patients.¹

Sedating antihistamines have more adverse effects but are useful if symptoms are causing sleep disturbance. The effect of adding a histamine H2-receptor antagonist or a leukotriene antagonist is not well established. Second-line agents include cyclosporine (which is reported to be effective in up to 75% of patients but may be associated with severe side effects) and short courses of oral corticosteroids. Intravenous

immunoglobulins and plasmapheresis have been reported to have beneficial effects in small trials only. Physical urticarias may respond to H1-receptor antagonists.¹⁵ Recently, case series^{21,22} and three randomized controlled trials²³⁻²⁵ have established a positive effect of omalizumab (a monoclonal antibody targeting IgE) in patients with chronic urticaria.

Noah's Case Continued

Noah received 150 mg of omalizumab subcutaneously and within 24 hours, hives resolved completely. In the following weeks he was able to taper his steroid dose and one month after his first omalizumab treatment, he was off steroids. He was treated with five additional monthly injections of omalizumab and currently has no clinical symptoms.

References

- Schaefer P: Urticaria: Evaluation and Treatment. *Am Fam Physician* 2011; 83(9):1078-1084.
- Hide M, Hiragun T: Japanese Guidelines for Diagnosis and Treatment of Urticaria in Comparison with Other Countries. *Allergol Int* 2012; 61(4):517-527.
- Ring J, Grosber M: Urticaria: Attempts at Classification. *Curr Allergy Asthma Rep* 2012; 12(4):263-266.
- Gregoriou S, Rigopoulos D, Katsambas A, et al: Etiologic Aspects and Prognostic Factors of Patients with Chronic Urticaria: Nonrandomized, Prospective, Descriptive Study. *J Cutan Med Surg* 2009; 13(4):198-203.
- Ring J, Grosber M: Urticaria: Attempts at Classification. *Curr Allergy Asthma Rep* 2012; 12(4):263-266.
- Pite H, Wedi B, Borrego LM, et al: Management of Childhood Urticaria: Current Knowledge and Practical Recommendations. *Acta Derm Venereol* 2013; April 2. doi: 10.2340/00015555-1573.
- Zuberbier T, Bindslev-Jensen C, Canonica W, et al: EAACI/GA2LEN/EDF Guideline: Definition, Classification and Diagnosis of Urticaria. *Allergy* 2006; 61(3):316-20.
- Maurer M, Weller K, Bindslev-Jensen C, et al: Unmet Clinical Needs in Chronic Spontaneous Urticaria. A GA(2)LEN Task Force Report. *Allergy* 2011; 66(3):317-330.
- Church MK, Weller K, Stock P, et al: Chronic Spontaneous Urticaria in Children: Itching for Insight. *Pediatr Allergy Immunol* 2011; 22(1 Pt 1):1-8.
- Maurer M, Weller K, Bindslev-Jensen C, et al: Unmet Clinical Needs in Chronic Spontaneous Urticaria. A GA(2) LEN Task Force Report(1). *Allergy* 2010; 66(3):317-330.
- Kaplan AP: Clinical Practice. Chronic Urticaria and Angioedema. *N Engl J Med* 2002; 346(3):175-179.
- Sahiner UM, Civelek E, Tuncer A, et al: Chronic Urticaria: Etiology and Natural Course in Children. *Int Arch Allergy Immunol* 2011; 156(2):224-230.
- Kozel MM, Mekkes JR, Bossuyt PM, et al: Natural Course of Physical and Chronic Urticaria and Angioedema in 220 Patients. *J Am Acad Dermatol* 2001; 45(3):387-391.
- Augey F, Gunera-Saad N, Bensaïd B, et al: Chronic Spontaneous Urticaria Is Not an Allergic Disease. *Eur J Dermatol* 2011; 21(3):349-353.
- Kozel MM, Sabroe RA: Chronic Urticaria: Aetiology, Management and Current and Future Treatment Options. *Drugs* 2004; 64(22):2515-2536.
- Kaplan AP, Greaves M: Pathogenesis of Chronic Urticaria. *Clin Exp Allergy* 2009; 39(6):777-787.
- Doutre MS: Chronic Urticaria and Thyroid Auto-immunity. *Clin Rev Allergy Immunol* 2006; 30(1):31-37.
- Altrichter S, Peter HJ, Pisarevskaja D, et al: Mediated Autoallergy Against Thyroid Peroxidase — A Novel Pathomechanism of Chronic Spontaneous Urticaria? *PLoS One* 2011; 6(4):e14794.
- Bagnasco M, Minciullo PL, Saraceno GS, et al: Urticaria and Thyroid Autoimmunity. *Thyroid* 2011; 21(4):401-410.
- Ben-Shoshan M, Blinderman I, Raz A: Psychosocial Factors and Chronic Spontaneous Urticaria: A Systematic Review. *Allergy* 2013; 68(2):131-141.
- Kaplan AP, Joseph K, Maykut RJ, et al: Treatment of Chronic Autoimmune Urticaria with Omalizumab. *J Allergy Clin Immunol* 2008; 122(3):569-573.
- Groffik A, Mitzel-Kaoukhov H, Magerl M, et al: Omalizumab — An Effective and Safe Treatment of Therapy-resistant Chronic Spontaneous Urticaria. *Allergy* 2011; 66(2):303-305.
- Saini S, Rosen KE, Hsieh HJ, et al: A Randomized, Placebo-controlled, Dose-ranging Study of Single-dose Omalizumab in Patients with H1-antihistamine-refractory Chronic Idiopathic Urticaria. *J Allergy Clin Immunol* 2011; 128(3):567-573.
- Maurer M, Altrichter S, Bieber T, et al: Efficacy and Safety of Omalizumab in Patients with Chronic Urticaria who Exhibit IgE Against Thyroperoxidase. *J Allergy Clin Immunol* 2011; 128(1):202-209.
- Maurer M, Rosen K, Hsieh HJ, et al: Omalizumab for the Treatment of Chronic Idiopathic or Spontaneous Urticaria. *N Engl J Med* 2013; 368(10):924-935.



Dr. Moshe Ben-Shoshan is a Pediatric Allergy and Immunology Specialist at Montréal's Children's Hospital in the Division of Allergy and Clinical Immunology, Department of Pediatrics, and at the Institut de recherche du Centre universitaire de santé McGill at McGill University in Montréal, Québec.

cme