TRAINEE ARTICLE

Chronic Idiopathic Urticaria in a Young Male

Rachel M Coleman, MD[1]; Kathryn Elizabeth Wheeler, MD[1]; Amy Wells[2]
[1]Clinical Assistant Professor, University of Florida College of Medicine
[2]Medical Student, University of Florida College of Medicine

ABSTRACT

Chronic idiopathic urticaria (CIU) is defined as urticaria, angioedema, or both that occurs without a known trigger and persists for greater than 6 weeks. CIU is a relatively common hypersensitivity disorder in childhood. Treatment is difficult as up to half of patients don't respond to traditional medications for urticaria. CIU can have a significant impact on quality of life, including increased rates of psychiatric disorders that often are untreated or unrecognized. Here we present a case report of a patient suffering from both CIU and anxiety where the urticaria was unresponsive to second generation antihistamines but improved with the tricyclic antidepressant, doxepin.

KEY WORDS

Chronic idiopathic urticaria, anxiety, doxepin

INTRODUCTION

Urticaria is defined as transient, pruritic wheals surrounded by an erythematous base that typically last less than 24 hours.[1,2] An estimated 20% of people will experience an episode of urticaria at some point in their lifetime, but chronic urticaria, lasting a minimum of 6 weeks, is reported to have a point incidence of 0.1-0.3% of children, with some estimates as high as 1.8%.[3,4,5] The types of chronic urticaria are differentiated by the trigger associated with the disease (such as heat, cold, pressure, vibratory, cholinergic, contact, or aquagenic), however an estimated 75% of patients with chronic urticaria have no specified trigger, termed chronic idiopathic urticaria (CIU).[2] Of those cases termed CIU, there may be an underlying autoimmune mechanism in up to 50% of cases[5,6], leading many to subgroup CIU into truly idiopathic and autoimmune mediated. The treatment of CIU is very challenging due in part to an unclear etiology in many cases. One study reports the mean time to resolution of CIU in children at approximately 20 months, while another study indicates approximately 9 months.[5,8] Additionally, the often unpredictable and

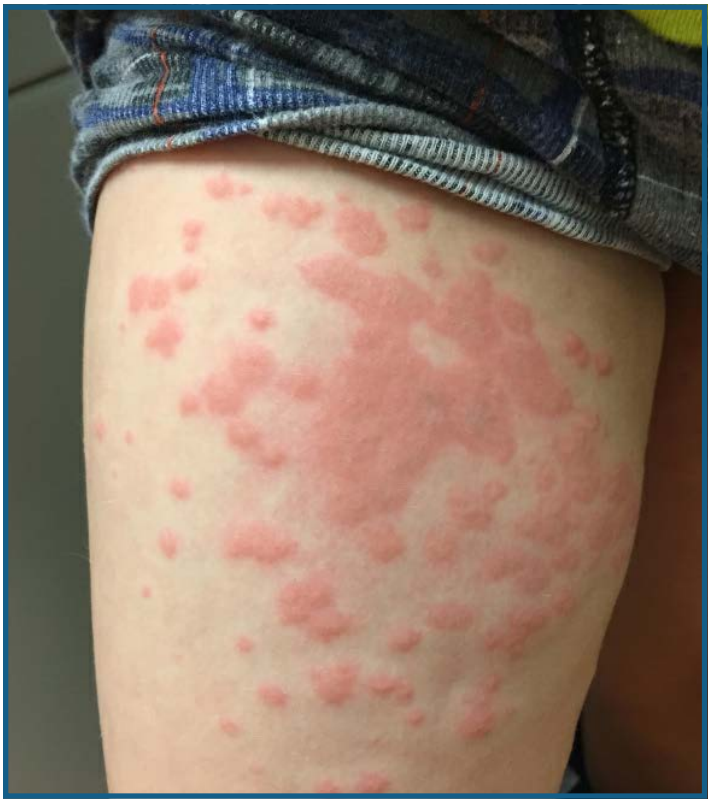
variable nature of episodes can lead to a sense of loss of control in patients, with many reporting decreased quality of life due in part to fatigue, sleep disturbances, pain, self-imposed social restrictions, and emotional turmoil.[9,1,2,10] This disease also has an impact on mental health, with higher levels of stress reported, along with increased incidence of psychiatric disorders, most notably anxiety and depression.[10,11] Here we present a case report of a patient suffering from CIU and anxiety whose symptoms of urticaria were unresponsive to second generation antihistamines but improved with the tricyclic antidepressant, doxepin.

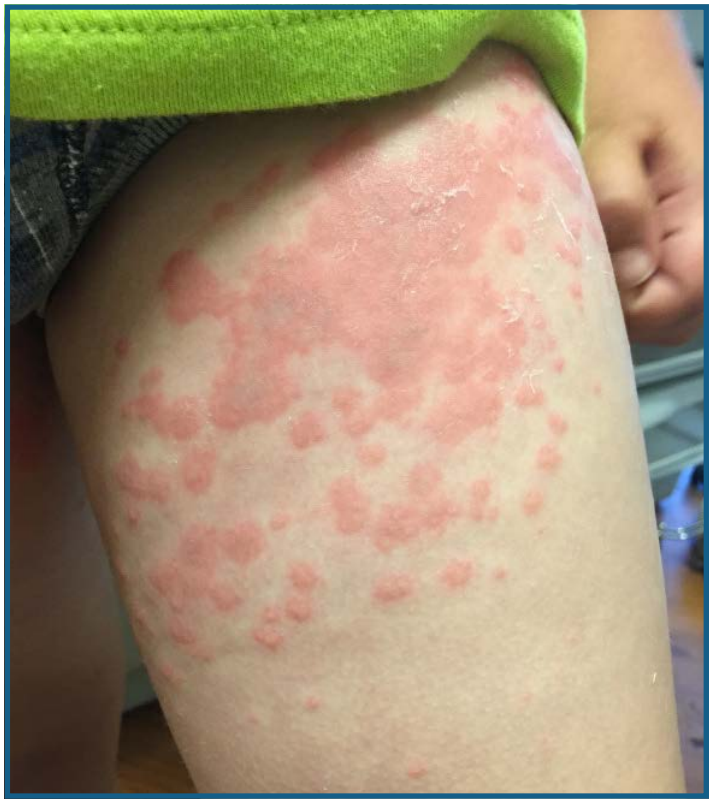
CASE REPORT

A 7-year-old male with a past medical history of asthma, eczema, and allergic rhinitis presented to the clinic with recurrent episodes of transient, erythematous, pruritic, blanchable wheals that were increasing in frequency over the last year. The patient has a family history of systemic lupus erythematosus in his mother, and extensive history of asthma, allergy, and eczema on his paternal side, including his father. The patient's first episode of wheals occurred across the hands, neck, and back after administration of ibuprofen following a tonsillectomy. Due to the timing and lack of other symptoms or sick contacts, the rash was determined to be consistent with allergic reaction. The patient was given an antihistamine and instructed to stop ibuprofen.

Approximately 6 months later, the patient experienced another episode of hives, which resolved with diphenhydramine treatment over a 10-day period. Two months following that episode, he presented to the emergency department with a 3-day history of wheals mostly on the trunk, legs, and face that did not respond to diphenhydramine or loratadine. With no new contacts or medications, and no fever or difficulty breathing, he was diagnosed with urticaria of unknown etiology and given prednisone 20 mg in the morning and 10 mg in the evening for 3 days. Lesions cleared within 1 day of administration of the steroid.

Over the next 3 months, the patient's mother noticed an increased frequency of hives, now occurring weekly. Of note, the hives had become persistent following a diagnosis of molluscum contagiosum with a superimposed *Staphylococcus aureus* infection 3 months ago. Additionally, the hives were now unresponsive to antihistamines, requiring low-dose steroids on two separate occasions. While there was no location predilection, the rash most commonly occurred over the patient's medial thighs and flexural areas. There were never symptoms of angioedema, gastrointestinal issues, breathing difficulties, joint pain or swelling, or sleep disturbances. The patient's mother did not notice correlation of recurrence of the hives with the common triggers of heat, cold, exercise, or compression. At the time of presentation at our clinic, the patient was currently taking loratadine 10 mg every morning and hydroxyzine HCl 5 mg every evening along with applying desonide 0.05% ointment during recurrence of hives, as prescribed by his pediatrician. The patient was also taking albuterol and beclomethasone for his asthma, as well as montelukast 4 mg nightly for his allergic rhinitis and asthma. A consult to UF Health Dermatology and a pediatric allergist was placed by his pediatrician to rule out other systemic disorders due to the increasing severity.





At this time, the patient presented with edematous erythematous wheals of variable size and shape diffusely across his body that were blanchable and warm to touch. Several lesions across the patient's thigh had faded to purple. While diagnosed with chronic urticaria, the differential for the cause of his chronic urticaria included urticarial vasculitis and hypocomplementemic urticarial vasculitis due to the presence of bruising following the resolution of some wheals. Other causes of chronic urticaria were eliminated based on history, including aquagenic urticaria, cholinergic urticaria, cold urticaria, delayed-pressure urticaria, dermatographic urticaria, exercise induced urticaria, solar urticaria, and vibratory angioedema.

Laboratory studies for a chronic urticaria panel were drawn including total IgE, C1, C2, C3, C4, and CH-50, along with Tryptase, CBC and differential, and ESR, all of which were normal. Due to the patient's history of allergic rhinitis, an ImmunoCAP® to environmental triggers was also performed, with negative results. As the episodes of wheals had increased in frequency and duration while on his current medication, he was started on cetirizine 5 mg every morning and 5 mg nightly along with continuing hydroxyzine 5 mg nightly and loratadine 10 mg every morning.

Upon further consultation, the mother noted persistent bruising on areas where wheals had resolved, resulting in a consult to pediatric rheumatology to rule out a vasculitic cause of his urticaria. He was also started on doxepin 35 mg every evening in place of the hydroxyzine. As the hives were improving, the dose of doxepin was changed to 50 mg every night as needed for breakthrough symptoms while continuing the cetirizine 5 mg twice a day.

Based on the history, physical presentation, and lab reports, a diagnosis of chronic idiopathic urticaria without clinical signs of urticaria vasculitis was made. As 40% of children with chronic idiopathic urticaria may develop an autoantibody to IgE, further blood tests were recommended for the future. Additionally, a thyroid panel including TSH, free T4, thyroglobulin antibody, and thyroid peroxidase, was ordered to evaluate for autoimmune thyroid disease as a cause for his urticaria, as thyroid autoimmunity can occur in up to one-third of patients.[1] The patient was continued on loratadine once a day, doxepin at night, cetirizine twice a day, and hydroxyzine as needed, with a plan that if the disease is not well controlled by this regime, cyclosporine would be considered the next-line agent for treatment.

DISCUSSION

With only 30-55% of patients achieving spontaneous remission within 5 years[12], urticarial symptoms have been shown to have a profound impact on everyday life for patients. Notably, more than 50% of patients report experiencing problems with daily living[2], citing issues of fatigue, pain, and itching, as well as emotional upset, withdrawal from social activities, and worsening performance in school.[9,13,12] Multiple studies have also shown an association between stress, psychiatric comorbidities, and CIU.[11,12] Therefore, while typically considered a dermatologic disorder, some physicians are now considering CIU to be a psychodermatological disorder due to the important role mental health and the stress response plays in the course of the disease.[14,15] Patient studies report that 81% of patients with CIU believed their illness was due to stress[11], with the unpredictable nature of episodes and difficulty in treatment mentioned as detrimental factors to the psychological well-being of patients.[15] The most common psychiatric diagnoses in CIU patients are depression, anxiety, and somatoform disorders, with as many as one-half of patients experiencing a psychiatric comorbidity.[10,11] Pediatric patients seem particularly vulnerable to developing concurrent emotional or behavioral difficulties due to stress because of underdeveloped coping strategies.[16] One study in children with CIU found that 70% had psychiatric comorbidities, indicating higher levels than the 49% and 60% that have been found in adult studies.[17] This study also showed that children diagnosed with CIU who had a previous stressful life event had a higher frequency of psychiatric disorders, possibly indicating that children with CIU may be prone to stress and thereby psychiatric disorders, or that stressful life events can serve as a trigger for already susceptible children.[17]

Treatment has always been a tenuous task for clinicians treating CIU as about half of patients fail to respond to traditional doses of H1-receptor antagonists and sometimes require up to four times the labelled dose.[18] Traditionally, treatment involves using second generation antihistamines as first line therapy with refractory cases using H2-antihistamines, anti-leukotrienes, immunosuppressive drugs, and anti-IgE antibody.[19] However, due to the discussed psychological associations, treatment with agents such as doxepin that have both antihistamine and antidepressant properties may be beneficial to consider. In our patient, doxepin was the treatment option that proved to provide the biggest relief from symptoms after resistance to the typical first line of anti-histamines. Doxepin has been shown to be a beneficial therapy for difficult to treat CIU since 1986[20], with two double-blind studies showing doxepin as more effective in clearing lesions than diphenhydramine in difficult to treat CIU.[18,20] While it is a tricyclic antidepressant, the major effect of doxepin as a treatment for CIU is thought to be due to the potent antagonism of H1 and some H2 receptors.[18] In light of the association of CIU with psychiatric disorders however, what has yet to be considered is the effect of doxepin acting as a tricyclic antidepressant on the psychiatric comorbidities of those with CIU. However, the use of doxepin needs to be both carefully considered and monitored, as all antidepressants have a FDA black-box warning for increased risk of suicidal thinking and behavior in children with major depressive disorder and other psychiatric disorders.

As more research indicates the association between psychiatric disorders, stress, and CIU, the use of agents such as doxepin may be considered sooner in these patients, in conjunction with the standard regime of antihistamines and steroids. Only one study[22] was found that used psychotropics in conjunction with antihistamines, therefore, more research is needed in order to determine the effect of appropriate psychiatric interventions as a more integrated approach may be necessary in children and parents trying to manage CIU. Furthermore, other psychological therapies outside of medication may be considered as well. While no studies have indicated a causal role of stress or psychiatric comorbidities in urticaria development at this point, one meta-analysis concerning adult patients reported a beneficial effect of psychological interventions across other skin conditions, including atopic dermatitis, that similarly have a large impact on quality of life.[23] Even though multiple studies have mentioned the association between psychological comorbidities and CIU, no rigorous studies were found that examined whether more intensive psychological interventions led to improved outcomes in pediatric patients with CIU, indicating an important potential area of treatment that has yet to be addressed.

CONCLUSION

At this point in time, the lack of research into the association between CIU and psychological health constrains our understanding of this disease, even more so in the pediatric population. While the evidence is still uncertain as to whether psychological factors are a cause or result of CIU, the high prevalence in patient populations indicates they may play an important role in the disease process and should be taken into account in terms of management and treatment of CIU. Therefore, the use of agents such as doxepin that have both immunological and psychiatric modes of action may be beneficial to consider in CIU. Additionally, an interdisciplinary effort that also includes psychiatric management may be beneficial for the treatment of CIU and further research is needed to better determine appropriate psychiatric interventions.

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