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## **Chronic Urticaria in Children: Expanding the "Autoimmune Kaleidoscope"**

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## EXPERIENCE AND REASON—Briefly Recorded

"In Medicine one must pay attention not to plausible theorizing but to experience and reason together. . . . I agree that theorizing is to be approved, provided that it is based on facts, and systematically makes its deductions from what is observed. . . . But conclusions drawn from unaided reason can hardly be serviceable; only those drawn from observed fact." Hippocrates: *Precepts*. (Short communications of factual material are published here. Comments and criticisms appear as letters to the Editor.)

### Chronic Urticaria in Children: Expanding the "Autoimmune Kaleidoscope"

**ABSTRACT.** Most cases of chronic urticaria (CU) are considered idiopathic. It has recently been accepted that autoimmunity plays a critical role in the pathogenesis of CU in some of these patients. Although urticaria is common in the pediatric population, the knowledge regarding CU-associated autoimmunity is very limited.

We describe the association of CU with a wide spectrum of clinical and laboratory autoimmune disorders in 2 children and emphasize the concept that CU is another manifestation of the "autoimmune kaleidoscope." *Pediatrics* 2000;106:1139–1141; chronic urticaria, autoimmunity.

ABBREVIATIONS. CU, chronic urticaria; IgE, immunoglobulin E; F<sub>Cε</sub>RI, IgE receptor; IDDM, insulin-dependent diabetes mellitus; Hb, hemoglobin; ESR, erythrocyte sedimentation rate; ANA, antinuclear antibodies; TSH, thyroid-stimulating hormone; JRA, juvenile rheumatoid arthritis; GFD, gluten-free diet.

Chronic urticaria (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.<sup>1</sup> A current theory is that CU might be autoimmune in origin, at least for a subpopulation of patients. Several lines of evidence support this concept. The frequency of atopy in these patients is equal to the general population, and the serum immunoglobulin E (IgE) is usually normal. Histopathologic biopsies of lesions of CU reveal a perivascular accumulation of eosinophils, mast cells, and activated CD4<sup>+</sup> T cells, in contrast to biopsies of lesions in acute urticaria, which are devoid of cellular infiltrates.<sup>2,3</sup> Recently, an increased incidence of anti-IgE and/or specific autoantibodies against the high-affinity IgE receptor (F<sub>Cε</sub>RI) on mast cells has been demonstrated in the serum of patients with CU.<sup>4,5</sup> Matthews<sup>6</sup> hypothesized that autoimmunity may play a role in some cases of CU. Subsequently, Leznoff and Sussman<sup>7</sup> reported that 90 (14%) of 624 patients who presented with CU had evidence of thyroid autoimmunity as compared with 3% to 6% of controls. Since then, many others have reported the

association of CU with various types of autoimmune diseases in the adult population, including celiac disease, insulin-dependent diabetes mellitus (IDDM), ulcerative colitis, and others.<sup>8–10</sup>

Information regarding the association of CU with autoimmunity in children is rare. We describe 2 children with CU associated with different autoimmune diseases.

#### CASE REPORTS

##### Case 1

A 15-year-old female was referred from the Endocrinology Unit, where she had been followed-up for the last 4 years because of IDDM, for evaluation of CU. She reported daily outbreaks of pruritic erythematous wheals of various sizes, each lasting up to a few hours without scarring or purpura, for the last 7 years. No angioedema was noted. Urticaria was aggravated by warm water and exercise. No specific foods or environmental allergens were implicated. Currently, she receives twice-daily injections of humanized insulin with reasonable control of her glucose and hemoglobin (Hb) A1C levels. Family history was negative for IDDM, thyroid disorders, CU, or other disorders suggestive of autoimmune disease. Physical examination was unremarkable. Laboratory investigations were negative for multiple food and aeroallergen prick tests. The erythrocyte sedimentation rate (ESR) was 10 mm/hr, and blood count was normal. Serum electrolyte values and liver functions were within normal limits. Test for antinuclear antibodies (ANA) was positive at a titer of 1:40, but with normal values of C<sub>3</sub> and C<sub>4</sub>. The patient had normal free T<sub>4</sub>, thyroid-stimulating hormone (TSH), and antiperoxidase antibody, but antithyroglobulin was 79.1 IU/mL (normal up to 26). Screening for other autoimmune markers revealed positive results for anticardiolipin antibodies 9 U/mL (normal 0–6) and antismooth muscle (1:20). At the present time, her CU is under control with a combination of H<sub>1</sub> and H<sub>2</sub> receptor antagonists.

##### Case 2

A 13-year-old boy was admitted to the Pediatric Department because of high fever, myalgia, and an urticarial rash for the last 10 days. His past medical history was positive for removal of a right double collecting system at 1 year of age and psoriasis since the age of 10 years. In addition, he reported daily itchy hives of various sizes for the last 2 years. The hives occurred evenings and nights, each lesion lasting up to a few hours. There was occasional angioedema of his face as well. His family history is strongly positive for autoimmune disorders. One sister has IDDM and celiac disease, while the other sister has euthyroid Hashimoto's thyroiditis. In addition, his mother and a maternal aunt have hypothyroidism. On admission, his physical examination was normal except for flare-ups of his urticaria. Laboratory studies showed an ESR of 10 mm/hr and normal blood count and liver and kidney tests. Throat, urine, stool, and blood cultures were all negative. A chest radiograph was normal. Over the next 13 days, he continued to have spiking fever up to 40°C with shaking chills, his weight dropped 3.5 kg, and a new onset of hepatosplenomegaly was noted. Repeated laboratory investigations revealed normocytic normochromic anemia (Hb: 10.2 g/dL) and ESR gradually increasing to 95 mm/hr. Serology tests and cultures for numerous viral, bacterial, and parasitic causes were all negative. ANA, C<sub>3</sub>, C<sub>4</sub>, and rheumatoid factor were all normal. Bone scan, chest and abdominal computed tomographic scans, bone marrow aspira-

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tion, and echocardiography were normal, as well as slit lamp and fundoscopic examination of the eyes. On his 11th day of hospitalization, he complained of pain in the neck, wrists, and right knee without any swelling. The next day a salmon-colored macular rash was evident on his trunk, and a diagnosis of systemic-onset juvenile rheumatoid arthritis (JRA) was presumed. Prednisone (20 mg twice daily) was started, and an immediate response was noted. The fever, bone pain, and urticarial lesions resolved within 24 hours. His appetite gradually returned to normal, and he gained 4 kg. Hb and ESR normalized within 2 and 5 weeks, respectively. Currently, he is in remission, still requiring low-dose steroids (prednisone 5 mg, alternate day).

## DISCUSSION

Most cases of CU are considered idiopathic, as no precipitating cause can be identified in >80% of cases. Although the mechanisms responsible for CU are not fully understood, it has recently been accepted that autoimmunity plays a critical role in the pathogenesis of CU at least for a subpopulation of patients. Hide et al<sup>5</sup> and other investigators<sup>11,12</sup> reported that up to 60% of patients with CU have autoantibodies directed to the Fc $\epsilon$ RI  $\alpha$  subunit. Furthermore, these autoantibodies were able to release histamine (the major mediator in urticaria) from human basophils and to activate rat basophil leukemia cells that were transfected with the  $\alpha$  subunit of Fc $\epsilon$ RI.<sup>12</sup> The concept that CU is another manifestation of autoimmunity is also supported by: a) the association of CU with a variety of autoimmune diseases<sup>7-10</sup> and b) the fact that patients with autoantibodies and severe CU, who do not respond to antihistamine treatment or are dependent on oral steroids, can benefit from immune-modulating modalities, such as plasmapheresis,<sup>13</sup> intravenous immunoglobulin,<sup>14</sup> and cyclosporine.<sup>15</sup>

Although urticaria is common in the pediatric population, the information regarding CU in children is limited and only a few reports have been published on this subject. Volonakis et al<sup>16</sup> investigated 226 children with CU. Causal factors were identified in approximately 20% of patients, including physical factors, infections, aeroallergens, food additives, and drugs. In another study,<sup>17</sup> CU was attributed to pseudoallergens, such as coloring agents and preservatives, in 12 (75%) of 16 children with CU. Interestingly, autoimmunity was not associated with CU in any of the cases outlined in these reports. Harris et al<sup>18</sup> studied 94 children with CU, and a cause was identified in 15 (16%) cases. These included patients with cold urticaria, infection, and food allergy. Two cases of CU associated with autoimmunity were noted. One patient had JRA and another had arthralgia and a positive ANA.<sup>18</sup>

Autoimmune diseases are a heterogeneous group in which a cause has not been yet identified, but it has been shown to reflect a complex interplay between environmental and genetic factors, especially MHC genes. There are at least 2 possible explanations for the wide spectrum of autoimmune manifestation that can be observed, sometimes in the same patient. The first one is that the immune dysregulation caused by the antigen in a specific disease may secondarily affect other organs. This mechanism was the one suggested by Hautekeete et al<sup>19</sup> and Gallo et al<sup>9</sup> when they described the disappearance of CU 3 to

6 months after the administration of gluten-free diet (GFD) for 2 adult patients who suffered from celiac disease associated with CU. The same mechanism was adopted by Naveh et al,<sup>20</sup> who reported the complete recovery of generalized alopecia in 2 of 3 patients with celiac disease 10 to 24 months after the institution of GFD and by Rumbly et al,<sup>8</sup> who reported the resolution of CU in patients with thyroid autoimmunity after treatment with thyroxine was introduced.

Although this mechanism can be a reasonable explanation for a subgroup of patients with autoimmune diseases, it cannot be the cause for the whole spectrum of autoimmunity. A second possibility is that a general immune disruption can affect several organs independently in a manner similar to the association of diseases in the polyglandular autoimmune endocrinopathies.<sup>21</sup> Indeed, the findings in our patients and their families support this concept.

The patient with IDDM did not show any improvement of her CU despite reasonable control of her glucose and Hb A1C levels. Interestingly, she has other markers of autoimmunity, such as positive ANA and anticardiolipin antibodies with no clinical significance. The same pattern of independency was noticed in a previously reported case of our child with CU, celiac disease, and thyroid autoimmunity.<sup>22</sup> The patient did not show any improvement of her CU even after strict GFD for >18 months, despite marked weight gain and disappearance of antinuclear antibodies. The second case demonstrated the most spectacular view of the autoimmune kaleidoscope. He sequentially developed 3 autoimmune diseases (psoriasis, CU, and JRA). His sister has both celiac disease and IDDM, while the other sister, his mother, and a maternal aunt all have autoimmune thyroiditis. These clinical observations support the hypothesis that CU is another marker of autoimmunity in a genetically susceptible individual, rather than a secondary manifestation of chronic immunologic inflammation in another organ.

The 2 cases described here together with our previously reported case expand the spectrum of autoimmune diseases associated with CU in children, emphasizing the importance of autoimmunity as a possible cause for CU not only in adults, but also in the pediatric population. Physicians following CU patients should be aware of these associations and screening of patients with CU for underlying autoimmune diseases should be considered.

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Frankford DM, Patterson MA, Konrad TR. Transforming practice organizations to foster lifelong learning and commitment to medical professionalism. *Acad Med*. 2000;75:708

Submitted by James W. Kendig, MD

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