

EDITORIAL

Chronic Urticaria in Children

Still Itching for Insight

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Six years ago, we reviewed what was then known about chronic urticaria (CU) in children.¹ We came to the conclusion that many important and interesting questions were unanswered. These included, but were not limited to, how common chronic spontaneous urticaria (CSU) and inducible urticaria are in children, the clinical presentation, underlying causes, impact on everyday life of CU in children, and the natural course of pediatric CU. We also suggested strategies to address and answer these questions and encouraged further studies to do so.

We Are Making Progress

Over the past 6 years, numerous studies on CU in children were performed and reported. For some of the questions we asked in 2011, we now have the first answers. For example, a



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Korean population-based study² found the prevalence of CU in children to be 1.8%.

A meta-analysis of studies on the causes of CU in children by Caffarelli and coworkers³ showed, among other interesting findings, that a high number of pediatric patients with CU exhibit features of autoreactivity, such as mast cell-activating autoantibodies. This, and other studies, have resulted in practical recommendations for the treatment of CU in children.^{4,5}

Regarding the natural course of CU in children, we have learned from Sahiner and coworkers⁶ that spontaneous remission occurs in 17%, 39%, and 50% of pediatric patients with CSU after 1, 3, and 5 years, respectively. Similar rates were reported by Chanskulporn and coworkers,⁷ with 20% of children with CU showing spontaneous remission within the first year, and one-half and two-thirds of them within 3 and 5 years after the onset of disease, respectively. Two years later, Eser and coworkers⁸ provided further confirmation of this, with their report that one-third and one-half of children with CSU show spontaneous remission within 1 and 3 years, respectively. The same study also showed that, similar to CSU in adults, time to remission is linked to disease activity; that is, faster remission occurs in children with CSU controlled by a standard-dosed antihistamine. This finding was confirmed this year by a study of Arik Yilmaz and coworkers⁹ that showed high urticaria activity score values to be associated with longer times to remission.

What Predicts the Duration of CU in Children?

The current report by Netchiporouk et al¹⁰ in this issue importantly adds to these findings. According to their results, children with CU show rates of resolution of around 10% per year. More importantly, they found that pediatric patients with CSU

with basophil-activating serum activity and low blood basophil counts show markedly earlier disease resolution than those without.¹⁰ In an earlier report,¹¹ this team showed that positive CD63 basophil activation tests, that is, basophil-activating serum activity, are common in children with CSU and linked to high disease activity.

What Have We Learned?

The current findings are important for several reasons: (1) Together with the results of previous studies, they allow physicians to provide children with CU and their parents with an educated guess on how long it will take until the disease goes away by itself. (2) While we still do not have good predictors for the duration of CU in individual children, we are beginning to understand that clinical features (eg, good response to antihistamine treatment) and laboratory markers (eg, basophil numbers and serum autoreactivity) can help to distinguish between subpopulations of pediatric patients with CU that differ in the duration of their disease. Although this observation is new, it is hardly surprising. In adult patients with CSU, laboratory markers and clinical features, such as higher age at onset, being female, long disease duration, hypersensitivity to aspirin and nonsteroidal anti-inflammatory drugs, comorbid inducible urticaria, or concomitant recurrent angioedema, have long and often been linked to longer CSU duration.^{12,13} What comes as a surprise is that, in children with CU, basophil-activating serum activity and basopenia, which are both linked to the presence of mast cell-activating autoantibodies and high disease activity, are associated with earlier, not later, disease resolution. This seems to contradict the findings that high disease activity, that is, failure to respond to a standard-dosed antihistamine⁸ or high urticaria activity scores,⁹ predict longer disease duration. (4) That both basopenia and autoreactive serum are linked to shorter times to remission in children with CU may point to the possibility that type 2 autoimmune urticaria (driven by IgG autoantibodies) is of shorter duration than type 1 autoimmune urticaria (driven by IgE autoantibodies), in children as well as in adults with CSU.¹⁴

Unanswered Questions

The current findings, like all important and interesting findings, also cause us to ask new questions. Future studies need to assess basopenia, basophil-activating serum activity, and other markers of "autoimmune" CSU for their link to the duration of disease. Such studies should be performed in children and adults with CSU. They should include, aside from blood basophil levels and serum autoreactivity, clinical fea-

tures of CSU previously linked to “autoimmune” CSU, such as comorbid autoimmune disorders, concomitant angioedema, and levels of disease activity, impact, and control, as well as blood levels of IgG-anti-FcεRI, IgG-anti-IgE, IgE-anti-self, other autoantibodies (eg, IgG-anti-TPO), autologous serum skin testing, total IgE, and response to antihistamines and omalizumab. Importantly, these studies should not only assess how these markers are linked to disease duration but also disease severity, age at onset, and sex ratios in patients with CSU. Other questions that emerge from the present findings include the following. What is the reason for the basopenia seen in some but not all patients with CSU? How is this linked to basophil-activating serum activity? Do basopenia and serum autoreactivity precede the development of clinical signs and symptoms, or do they result from them? Both antihistaminic therapy and treatment with omalizumab have been shown to normalize blood basophil levels in patients who benefit from these treatments. Is the same true for serum autoreactivity, and is spontaneous remission in patients with CSU linked to the loss of serum autoreactivity?

Approaches and Strategies for Future Research

Future research needs to address these questions as well as other unanswered questions on CU in children. Several initiatives may be helpful for doing this. The global chronic urticaria registry, CURE (<http://www.urticaria-registry.com>) allows for the identification, characterization, and comparison of

subgroups of CU, in pediatric and adult patients. Currently, data from around 1000 CU patients, including many pediatric patients, have been included in CURE. This registry is academia-driven, and all physicians who treat patients with CU are invited and encouraged to enter data from their patients. In 2011, we had launched the CUKid network, a consortium of researchers and clinicians interested in CU in children. This network has since merged with CURE, and CUKid members are actively contributing to the collection of pediatric CU data in this registry. Consortial efforts are more likely than those of individual urticaria centers to bring new insights to the treatment of pediatric CU, for obvious reasons. Networks provide a broader, global reach with larger patient populations and higher patient numbers available for analyses in less time. The GA²LEN Urticaria Centers of Reference and Excellence (UCARE) network (<http://www.ga2len-ucare.com>) seems ideally suited to support such network efforts.¹⁵ GA²LEN UCARE's aim is to jointly improve our knowledge and the awareness of CU, including pediatric CU, and the UCARE network encourages its current member centers and those who will join us in the future to make the investigation of pediatric CU a focus of their studies and research projects. The efforts and reports by Netchiporouk and coworkers¹⁰ and others are gratefully acknowledged and appreciated by the global urticariologist community. Let's keep up the good work and increase and coordinate our activities to better understand CU in children.

ARTICLE INFORMATION

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