

Problems to Be Resolved in the Management of Urticaria

Urticaria is one of the most common diseases, not only for dermatologists and allergologists, but also for primary care and many other medical practices. It can be very severe and even fatal, especially in cases of angioedema. However, many cases of urticaria are easy to treat, spontaneously remit, and may even be cured. On the other hand, it is difficult for us to answer a question raised by many patients, "what is the cause of my urticaria?", regardless of their disease severities and responsiveness to medications.

Diagnostic examinations may be useful for understanding the pathogenesis or for making a solid diagnosis, but these can be meaningless if performed without specific aims based on careful clinical observations. Measurement of antigen-specific IgE is commonly used for the diagnosis and the management of urticaria that has developed through type I allergy, but is of little use for spontaneous urticaria. Skin biopsy is essential for the diagnosis of urticarial vasculitis, but unnecessary to know the cause of urticaria induced by a systemic reaction against exogenous antigen for type I allergy. Thus, it is important for physicians to make a correct diagnosis of urticaria at the level of subtypes. For this purpose, the role of guidelines for urticaria with a full classification system is very important.

In 1997, the first urticaria guideline was published by a committee of EAACI for the classification and diagnosis of physical urticarias.¹ However, comprehensiveness, including treatments, is an important requirement for an urticaria guideline. In this sense, the first comprehensive guideline for urticaria was published by Grattan, *et al.* in 2001 on behalf of British Association of Dermatologists (BAD).² The Japanese Dermatological Association (JDA) published its first guideline for the diagnosis and treatment of urticaria and angioedema in 2005, and revised it in 2011.³ Also, the Japanese Association for Complement Research published a guideline for the diagnosis and treatment of hereditary angioedema (HAE) in 2010 on the website <http://square.umin.ac.jp/compl/HAE/HAEGuideline.html>. Both of these Japanese guidelines established or authorized most standard diagnoses and treatments of urticaria and HAE in Japan, respectively. Principles of the treatment for urticaria and angioedema are most likely the same all over the world. However, there are substantial differences in phenotypes, populations and responsiveness between patients in Japan and those in Europe and

North America. Therefore, it is our great pleasure to introduce these Japanese guidelines^{4,5} for urticaria and HAE, respectively, in this issue of Allergology International in English. The guideline published by JDA for the management of urticaria is unique in that it covers almost the entire spectrum of urticaria and angioedema and proposes a few comprehensive algorithms for the management of spontaneous urticarias. The option of medications is important, but the manner of its usage is equally or even more important for practices regarding the management of urticaria.

As causes of urticaria, foods⁶ and drugs⁷ are probably most frequently suspected by patients. In this issue, two articles have reviewed these topics. A dramatic increase in the number of patients with wheat-dependent exercise-induced anaphylaxis (WDEIA) in Japan since 2010 has become a nation-wide problem and has offered many important lessons and insights not only to the medical community in Japan, but also for our colleagues around the world. The development of WDEIA in association with hydrolyzed wheat protein has strongly suggested an important role of the skin with respect to sensitization for type I allergy. Moreover, the analysis of hypersensitivity of these patients has revealed the importance of antigen component analysis in food allergy.

The fifth topic in this issue is the role of hidrosis in the pathogenesis of cholinergic urticaria. Historically, this type of urticaria used to be included in the group of physical urticarias. However, the above mentioned recent guidelines for urticaria separate this urticaria from physical urticarias. Cholinergic urticaria is certainly different from physical urticaria in that its symptoms are induced by the stimuli that prompt sweating, such as an increase in body temperature and emotional excitations, which are not physical stimuli. Bito *et al.*⁸ have reviewed recent progress in the understanding of this unique urticaria, especially concerning the aspect of acetylcholine and sweat allergy. Certain populations of patients with this type of urticaria may be associated with depressed sweating. Interestingly, 26 out of 29 patients with cholinergic urticaria and anhidrosis and/or hypohidrosis in the literature are Japanese. Another population of patients with cholinergic urticaria showed type I hypersensitivity against their own sweat, either by skin test and/or *in vitro* basophil stimulation tests. Such patients may be treated by subcutaneous injections of sweat antigens to induce tolerance. Molecular identi-

fication of human sweat antigen is expected not only to assist in the study of the pathogenesis, but also for the development of new therapies for this unique and often life disrupting subtype of urticaria.

Among 7 original articles and 1 letter to editor in this issue, Izuhara's group published two articles regarding periostin.^{9,10} Periostin is now widely recognized to be an important biomarker for diagnosing as to whether IL-13 or Th2 cells are highly involved in asthma and allergic disease. This new cytokine was originally found in microarray analysis done by these authors several years ago. In this issue, they report that periostin contributes to the pathogenesis of atopic dermatitis by inducing TSLP production from keratinocytes. Also, the same authors report that the levels of periostin are increased in samples obtained from allergic rhinitis and chronic sinusitis. We do hope that readers of this issue find these articles interesting and useful.

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