Symposium 1. Urticaria and angioedema

Angioedema in Japan

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Angioedema is a vascular reaction of the deeper layers of the skin and mucous membranes. It shows asymmetric, nondependent, and nonpitting edema and resolves without scarring or discoloration. Although the face, hands, feet, and genital region are affected, lip and periorbital swelling are the most common. Swelling of tongue, pharynx, and larynx is particularly problematic. Fatalities can occur because of laryngeal edema.

There are several types of angioedema, histamine mediated angioedema or bradykinin mediated angioedema. In the former cases, angioedema can be caused by allergic reactions caused by immunoglobulin E (IgE)-mediated hypersensitivity to foods or drugs that can also result in acute urticaria or a more generalized anaphylactic reaction. Angioedema also accompanies some chronic urticaria cases. Most of the Japanese cases have a history of atopic dermatitis, and show sweat allergy. Antihistamines are not sufficiently effective for this type of angioedema.

Bradykinin-mediated angioedema can be either hereditary or acquired. Hereditary angioedema (HAE) is an autosomal dominant inheritance. Mutations in the *SERPING1* gene, which codes for C1 inhibitor (C1-INH), are known to cause HAE. HAE dues to C1-INH deficiency can be further divided based on the C1-INH antigenic level: type I HAE is characterized by Low antigenic levels and type II HAE is characterized by normal /elevated antigenic but low functional C1-INH levels. HAE with normal antigenic and functional levels of C1-INH is type III. Mutations of the *FXII* gene have been identified in some families, but the pathophysiology is still undefined. The case of type III HAE has not been reported in Asian countries. The estimated prevalence of HAE in the general population is considered one individual per 50,000, with reported ranges from 1:10,000 to 1:150,000. On the other hand, a nation-wide prevalence survey of HAE in Japan reported only 52 patients, and a summary of reported HAE patients in Japan from 1969 to 2010 showed only 132 patients. According to the above mentioned nation-wide prevalence survey, HAE is mainly managed by dermatologists in Japan, and is not widely recognized among physicians except for

dermatologist. Thus, HAE might be often unrecognized or misdiagnosed in Japan, and the educational programs for the public and health-care professionals are necessary. The situation regarding the examinations for the diagnosis and the treatments of patients with HAE in the Asia Pacific is very different from that in Europe and North America. A diagnosis of C1-INH deficiency requires laboratory confirmation with measurement of the C4 level, C1-INH antigenic level, and C1-INH functional level. C4 is an excellent screening test for C1-INH deficiency; most patients with C1-INH deficiency have a reduced C4 level. Laboratory tests for diagnosis of HAE, including genetic analysis, are easily available in Japan. Regarding treatments during an attack, we give the patients concentrated C1-INH, but we don't have any self-administration therapy. We need self-administration drugs and new prophylaxis treatment of HAE.

In this symposium, I would like to focus on angioedema accompanied by cholinergic urticaria in Japan and the situation surrounding HAE in Japan.