

CORRESPONDENCE

Urticaria as a Presenting Prodromal Manifestation of Attacks of Hereditary Angioedema

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We read with great interest the recent paper by Rasmussen et al. (1). They reported that the incidence of erythema marginatum (EM), a skin rash considered to be a primary prodromal manifestation of hereditary angioedema (HAE), was as high as 56% and that EM was often misdiagnosed as urticaria in the 87 HAE patients analysed. The authors also showed that misdiagnosis of EM as urticaria delayed the diagnosis of HAE. Their findings support those of an earlier study by Magerl et al. (2).

For decades patients with HAE were considered not to have urticaria. On the other hand, we have previously stated that bradykinin-mediated angioedema cannot be ruled out solely on a positive medical history of urticaria (3). Rasmussen et al. retrospectively investigated the history of urticaria in their cohort. Twenty-two of 87 (25%) patients with HAE reported at least one episode of urticaria. Urticaria was acute, inducible (“physical”), or referred to as chronic spontaneous urticaria. However, the majority of the patients (16/22) presented urticaria of “unspecified” origin. The precise nature of, or factors triggering, urticaria in this particular group remain a matter of discussion. However, based on these findings and on our clinical experience (3), the lifetime incidence of urticaria may be higher in patients with HAE than in the general population. We therefore strongly question the dogma that “patients with HAE do not have urticaria”. Indeed we have seen several patients with prodromal manifestations of attacks of angioedema presenting as erythematous and oedematous pitting rather than pruritic papules (Fig.

S1¹). These observations suggest that some EM may present as or even be urticaria. The pathophysiology of EM, an odd erythematous rash in the context of a non-inflammatory condition, is not completely understood. Furthermore, there is a lack of data on the incidence of urticaria compared with other prodromal skin rashes in patients with HAE. This is an issue primarily concerning dermatologists, since they are probably the most capable of properly describing various types of skin rash in this context. Finally, it is also not clear why only a subset of patients with HAE may present with urticaria.

The increased vascular leakage in HAE is mostly due to formation of the peptide hormone bradykinin (BK). Mouse models have revealed that heparin released from allergen-activated mast cells triggers BK production and angioedema episodes in a kinin B2 receptor-dependent manner (4). Similarly, BK produced by the plasma contact system contributes in anaphylaxis and allergic diseases to increased vascular permeability, and this reaction cascade is also initiated by allergen-stimulated mast cells (5). Taken together, these findings indicate that oedema in patients with HAE may be precipitated by allergen exposure, emphasizing a role of mast cells in initiating BK-mediated oedema. They support the observation that mast cell-driven urticaria or urticaria-like manifestations do exist in patients with HAE. The lower frequency of allergic diseases in the general population (including patients with HAE) when HAE has been described could be an explanation for the statement that these patients were initially considered not to have urticaria. However, physicians must remain alert and aware that disease manifestations may be modified over time.

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Response to the Comment by L. Martin et al.

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We appreciate the comments from Martin et al. on our paper (1). We fully support their message, that bradykinin-mediated angioedema cannot be ruled out based on a positive medical history of urticaria. They illustrate this

statement by photographs of wheals occurring as prodromal manifestations of HAE attacks in 2 of their patients.

To our knowledge, this is the first report of such patients documented by photographs. Theoretically,

one way to investigate mast cell activation would be to measure serum-tryptase in the initial phase of an attack. However, this test may not be sensitive enough. Also, patients with EM do not have elevated tryptase levels (6).

Similarly, in our clinical experience, patients with another form of bradykinin-related angioedema, namely angiotensin-converting enzyme-inhibitor induced angioedema, might present with various rashes including ur-

ticarial eruptions (unpublished data). In addition, within this field, there is a clinical dogma that if an urticarial eruption is present the angioedema cannot be caused by the angiotensin-converting enzyme-inhibitor (7). Tai et al. (8), in one of the largest studies on this topic, found a rash to be present in almost 8% of patients presenting with angioedema due to angiotensin-converting enzyme-inhibitors or angiotensin II-receptor blocking agents (personal communication, unpublished data).

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