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CLINICAL REPORT

Urticaria and Prodromal Symptoms Including Erythema Marginatum in Danish Patients with Hereditary Angioedema

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Erythema marginatum is a characteristic skin rash seen in patients with hereditary angioedema (HAE); however, it can be confused with urticaria, leading to delay in correct diagnosis. The aim of this study was to clarify how often erythema marginatum is misinterpreted as urticaria, potentially leading physicians to refrain from testing for HAE. Few studies have been published on urticaria and prodromal symptoms in HAE, thus the incidence of these parameters were also investigated. A total of 87 patients affiliated to the national HAE Centre were included. Retrospective and prospective data on skin eruptions and prodromal symptoms were collected. Fifty-six percent of 87 patients had a positive history of erythema marginatum. Half of the patients had experienced erythema marginatum being misinterpreted as urticaria. The most prevalent other prodromal symptoms were other skin symptoms, malaise, psychological changes, fatigue and gastrointestinal symptoms. HAE patients with erythema marginatum have a longer diagnostic delay, presumably caused by misinterpretation of the rash as urticaria. ***Key words: hereditary angioedema; erythema marginatum; urticaria; prodromal symptoms.***

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Hereditary angioedema (HAE) is an autosomal dominant inherited disease with bradykinin-mediated skin swellings caused by a diminished level (type I) or function (type II) of complement C1 inhibitor (C1INH) due to mutations of the *SERPING1* gene (1). A third type of HAE with normal C1INH exists, which is often oestrogen-sensitive and may be associated with mutations of the *factor XII* gene, *F12* (2). HAE has been described in the medical literature since the 19th century, but only recently have effective treatment regimens been widely established (1, 3). Angioedema is the main symptom of HAE, but a wide range of associated and prodromal symptoms have been systematically reported in recent studies (4–6). Among these, the most specific symptom is erythema marginatum (EM), which has attracted special attention in the literature since the original report by Dinckelacker in 1882 (7). EM is a reticular and serpiginous, usually non-pruritic, erythema (Fig. 1), mostly located on the upper trunk that might precede or accompany angioedema, although it can also occur independently (8). This type of rash has also been observed in association with rheumatic fever (9). EM is distinct from urticaria, which is pruritic, transient and more widespread, often consisting of smaller or larger elevated wheals. The exact pathomechanism of EM is unclear, although it has been suggested that it is bradykinin-mediated (10, 11). Traditional anti-allergic treatment regimens have proven ineffective in HAE-related EM and angioedema.

It has long been a clinical dogma, that patients with HAE do not have urticaria, which might cause some clinicians to pre-exclude this important diagnosis when urticarial rash and angioedema occur together or the patient reports urticaria in the disease history (11–14). Misdiagnosis of EM as urticaria might therefore contribute to diagnostic confusion and significant delay in

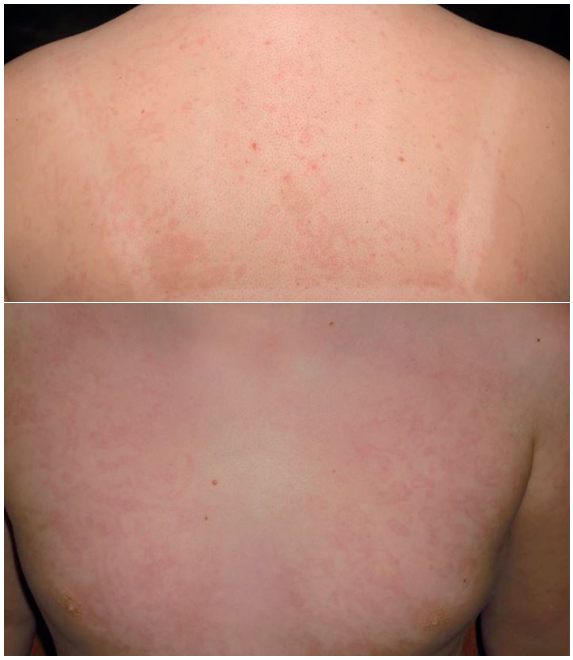

Fig. 1. Erythema marginatum. Erythema marginatum in two separate patients: back of a woman (top) and thorax of a young man (bottom).

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the diagnosis of HAE, leading to ineffective and potentially harmful treatment regimens with anti-histamines, glucocorticoids and/or adrenaline.

In this study we report the incidence of urticaria and prodromal symptoms, including EM, in a cohort of Danish HAE patients with a focus on diagnostic challenges of skin signs.

MATERIALS AND METHODS

Inclusion criteria were HAE type I or II and attendance at the national HAE Centre in Denmark. Eighty-eight HAE patients were included, but one patient had died at the time of follow-up and was excluded due to a lack of information, leaving 87 patients for data analysis. Adult patients provided written consent prior to participation in this study and parents provided written consent on behalf of their children. Although some patients had their initial HAE testing carried out at other health facilities, all patients had the diagnosis confirmed at the HAE Centre.

The study comprised 3 separate parts: (*i*) baseline data collection: at the first visit in the HAE Centre, patients completed purposely designed questionnaires with questions about skin eruptions, prodromal symptoms, treatment regimens and their effectiveness. The patients were assisted by a trained dermatologist in the process of completing the questionnaires. Special emphasis was put on the difference between EM and urticarial eruptions. Family history was explored and pedigrees were drawn in order to identify other possible HAE patients and assess the likelihood of hereditability or *de novo* mutation. Medical records from other hospitals were retrieved and reviewed when deemed relevant. (*ii*) Prospective data collection: once the patient was enrolled at the HAE Centre medical records were kept updated regarding symptoms, prodromes, treatment regimens, effectiveness, well-being and other relevant medical and social information. Furthermore, patients completed a HAE-specific diary, which was also used as an evaluation tool at each visit. (*iii*) Follow-up: in patients with a lack of information in their diaries (especially children), an e-mail was sent or a telephone call made at the end of 2013 or beginning of 2014 to retrieve updated information.

Microsoft Excel for Windows 8 and STATA version 13 were used for data analysis.

This study was approved by the Danish Data Protection Agency (number 2009-41-2987). In Denmark questionnaire studies are not required to be approved by an ethics committee. The study was conducted according to the principles of the Declaration of Helsinki.

RESULTS

Eighty-seven patients were identified, with a male:female ratio of 1.02 (Table I). Four children were still asymptomatic. Sixty-four patients (74%) could always or sometimes predict an upcoming attack, which meant that they had some kinds of prodromal symptoms. Forty-nine patients (56%) had experienced EM. A total of 22 patients (25%) reported former episodes of urticaria (cold urticaria, symptomatic dermographism combined with delayed pressure urticaria and chronic spontaneous urticaria) or events with urticarial lesions, which in 3 cases could be related to penicillin allergy or infusion of fresh frozen plasma (Table II). A total of 13 patients (27%) reported former episodes of EM as well as urticarial lesions. Half of all patients experiencing EM reported that EM has been misinterpreted as being urticaria by healthcare personnel primarily at the emergency department or by their general practitioner. In support of this finding, the mean diagnostic delay was almost 2 years longer in patients with EM. A high percentage of patients had been treated with anti-allergic medications before they were correctly diagnosed with HAE and these medications had little or no effect on EM or angioedema. However, patients who had both urticarial lesions and EM were, in most cases, not able to distinguish between the efficacy of anti-allergic treatment on their urticaria vs. EM, as, in the past, many were not aware of the differences between the 2 entities.

Seventy-eight patients answered additional questions concerning prodromal symptoms (Table III). The most

Table I. *Characterization of the Danish cohort of 87 patients with hereditary angioedema (HAE)*

Characteristics	
Patients, male/female, *n*	44/43
Male:female ratio	1.02
Age, years, median, (range)	41 (0–83)
HAE type I[a], *n* (%)	81 (93)
HAE type II[b], *n* (%)	6 (7)
Children <18 years old, *n*	17
Adults, *n*	70
Diagnostic delay, in patients without EM, years, mean	15.6
Diagnostic delay in patients with EM, years, mean	17.7
Can predict an oncoming attack, patients, *n* (%)	
Always before an attack	37 (43)
Sometimes	27 (31)
Never	12 (14)
Patient unsure	2 (2)
No verified attacks	4 (5)
Missing data	5 (6)

[a] 81 individuals from 29 families; [b] 6 individuals from 2 families.
EM: erythema marginatum.

Table II. *Urticarial eruptions and erythema marginatum (EM) in 83 symptomatic patients with hereditary angioedema*

History of EM, *n* (%)	
Yes	49 (56)
No	37 (43)
Patient unsure	1 (1)
Lifetime prevalence of urticarial eruptions, *n* (%)	
Yes	22 (25)
Penicillin allergy	2
Cold urticaria	1
Combined delayed pressure urticaria and dermatographism	1
Provoked by fresh frozen plasma infusion	1
Chronic spontaneous urticaria	1
Unspecified	16
No	63 (72)
No data	2 (2)
History of EM and urticarial eruptions, *n* (%)[a]	13 (27)
History of EM misinterpreted as urticaria, *n* (%)	
Yes	25 (29)
No	60 (69)
Patient unsure	1 (1)
No data	1 (1)

[a]Patients with erythema marginatum (EM). Numbers are rounded and therefore do not always add up to 100%.

frequent prodrome was EM, followed by tightness or a prickling sensation of the skin, pruritus, malaise, psychological changes, such as irritability and anxiety, fatigue and gastrointestinal complaints (nausea, vomiting, abdominal pain, diarrhoea, hunger, thirst, distended abdomen and abdominal discomfort). Only one patient below the age of 12 years could consistently report a prodromal symptom (headache).

DISCUSSION

To our knowledge, no previous studies have been carried out systematically to assess the lifetime prevalence of skin eruptions in a large cohort of HAE patients. In this cohort the incidence proportion (or cumulative incidence) of EM and urticaria or urticarial lesions were 56% and 25%, respectively. More than 1/4 experienced both features. Half of our patients with EM had their rash misinterpreted as urticaria at least once. Magerl et al. (14) recently demonstrated a statistically significant longer diagnostic delay in HAE patients experiencing EM. The diagnostic delay in our study was 2 years longer in patients with EM.

In a prospective study by Prematta et al. (15) the prevalence of hives as prodromal symptom varied from 4% to 25% depending on anatomical region. Patients might have used the term "hives" instead of EM, although investigators asked patients about "non-itchy rash with pale centres" suggestive of EM. In our study, the questionnaire was completed with the support of a dermatologist, emphasizing the differences between urticaria and EM. Also, patients with any "rash" had a clear sense of the differences in clinical presentation, e.g. itching or non-itching. Data is not directly comparable however, as we report "per-patient" rather than "per-attack" data. In a retrospective questionnaire-based survey of 46 patients with HAE, Prematta et al. (5) reported that 33% of patients described a rash on the trunk and 48% reported a rash on arms or legs before their most recent angioedema attack. Although no details regarding this sign were stated, one could presume that most patients described EM. A retrospective survey reported a lifetime prevalence of 42% regarding prodromal "rash" in 33 patients with HAE, but no further definition of the rash was made (6). Nielsen et al. (16) described "iris-like red and slightly elevated circles in the skin before or during attacks", presumably EM, in 50% of patients with HAE. Furthermore, they reported one child being hospitalized because of presumed urticaria. In our cohort a young boy was likewise hospitalized several times with angioedema and "viral rash", "erythema multiforme" and "allergy" (17). In this particular patient EM was observed for the first time when he was only a few weeks old and several years before he had his first swelling attack. This example highlights the need for C1INH testing when a diagnostic "clue", like EM, presents in patients without angioedema.

Table III. *Patients reporting prodromal symptoms including erythema marginatum (*n = *71); 53 patients experienced more than one prodromal symptom (why % does not add up to 100%)*

Symptoms	*n* (%)
Skin	
Erythema marginatum	49 (56)
Pressure, prickling sensation, tightness	32 (37)
Pruritus	12 (14)
Other, i.e. changed sensitivity	6 (7)
Malaise	23 (26)
Psychological changes (irritability and anxiety)	19 (22)
Fatigue	18 (21)
Gastrointestinal symptoms	14 (16)
Excessive perspiration or unpleasant body odour	5 (6)
Change in temperature perception	3 (3)
Dysuria (including "foul-smelling urine")	3 (3)
Headache	2 (2)

The main challenge when carrying out retrospective studies is recall bias. However, since 2001 we collected prospective data using patient diaries, which were upgraded to an extended version in 2013 made electronically in 2014.

The exact pathomechanism of EM is unknown. A single study demonstrated a localized accumulation of bradykinin in the stromal tissue and endothelial cells in a skin biopsy (11). This observation is supported by the clinical experience that traditional anti-allergic treatment regimens are not effective in EM or HAE in general. This subject needs further assessment.

One patient had symptomatic dermographism and delayed pressure urticaria, one patient had cold urticaria, 2 patients reported urticarial eruptions during penicillin treatment and one patient had chronic spontaneous urticaria. These numbers are comparable with the known incidences in the background population (18–20). Lifetime prevalence of urticaria in the general population has been stated to be approximately 20% (21). No data exist in the literature on urticaria incidence or prevalence in HAE populations, but in this study the lifetime prevalence of urticaria or urticarial lesions due to other medical conditions was (i.e. penicillin allergy, cold urticaria, pressure urticaria) 25%.

However, bradykinin-mediated angioedema should not be ruled out solely on the presence of a positive medical history for urticarial lesions (22). Recently interesting studies on murine C1INH knock-out models have revealed a possible role of subclinical mast cell activation in the initiation of attacks in patients with HAE. This could potentially predispose for urticarial eruptions and vice versa urticaria might activate angioedema in patients with HAE; however, further investigation is required (23, 24).

Increasing attention is being paid to prodromal symptoms of HAE, as the ability to foresee an oncoming attack is paramount in timely on-demand treatment. Regimens of home therapy enable the patient to treat attacks at an early stage to avoid progression of the oedema. Our study thus included data on prodromal symptoms other

than skin manifestations and showed that more than 90% of symptomatic patients with HAE experienced prodromal symptoms. In concordance with several other prospective and retrospective studies, we found a high prevalence of malaise (27%) and fatigue (21%) (5, 6, 25). Skin symptoms other than rash were also significant findings in our cohort (38%). In one prospective study the per-attack incidence of skin-related symptoms was significantly lower (15). Psychological changes have consistently been reported as prodromal features by patients with HAE, with a prevalence ranging from 15% in the literature to 21% in this study (6, 26). Symptoms related to the digestive tract were frequent in our study (17%) as in other reports (12–61%); prodromes related to the gastrointestinal system were especially found to precede abdominal attacks (5, 6, 15). This is predictable, since >50% of HAE attacks are located to the intestinal mucosa and an attack can be initializing for several hours causing abdominal discomfort. We suggest that these prodromes may, in fact, be signs of early swellings. In other studies joint and muscle pain were often reported, but that was not the case in our patient group (5, 6). This might, however, be due to lack of attention to these symptoms.

In conclusion, these results show that 50% of patients with HAE experiencing EM have the rash misdiagnosed as urticaria, even by medical personnel. This leads to inefficient treatment regimens with anti-allergic medications and may delay diagnosis of HAE. Also, more than 90% of patients with HAE experience prodromal symptoms; which may help patients and physicians to decide when to treat an oncoming attack. Further studies, preferably with a prospective design, are needed to elucidate these facts.

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