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Histamine-release test in angioedema patients without urticaria - a retrospective cohort study of 404 patients

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Summary
A subset of patients with angioedema (AE) and urticaria has histamine releasing autoantibodies. The histamine release test (HR-test) has been used as a tool in chronic urticaria to define the autoimmune subgroup and may possibly guide the clinician to a more personalized therapy, like omalizumab and cyclosporine. The prevalence and value of positive histamine releasing autoantibodies in monosymptomatic AE is sparsely described in the literature. The purpose of this study was to report the prevalence of positive histamine releasing autoantibodies in a cohort of patients with recurrent AE and evaluate the usefulness of this test in AE patients. We performed a retrospective cohort study of 612 patients referred due to AE between 1995 and 2013. HR-test results were available in 404 patients. In the sub-group of patients with AE and urticaria, 17.3% had a positive HR-test but only 4.3% of patients with mono-symptomatic AE had a positive HR-test. No statistically significant treatment benefits of antihistamines, corticosteroids or adrenaline were found comparing patients with angioedema +/- urticaria based on the result of the HR-test (negative / positive). Thus, the HR-test result cannot be used as predictor of the efficacy of anti-allergic treatment.

Introduction

Angioedema (AE) is a non-pitting skin colored swelling of skin or mucosa, with a predilection for areas with loosely bound skin. It is caused by a temporary increase in vascular permeability due to vasoactive mediators.
Mostly, AE is accompanied by urticaria, which indicates activation of mast cells liberating histamine and other vasoactive mediators. A subset of patients with urticaria and AE has histamine-releasing autoantibodies. The basophil histamine release test (HR-test) is a remedy to identify activation of basophils or mast cells causing histamine release. It has been used as a tool in chronic urticaria (CU) to define the autoimmune subgroup, and it is the current gold standard to detect histamine releasing autoantibodies to the FcεRI and less frequently against IgE (1,2).

Functional histamine releasing autoantibodies have been identified by the HR-test in approximately 20-30% of patients with CU (2-6). In contrast to CU or AE accompanied with urticaria, where histamine releasing autoantibodies can be frequently detected, sparse data can be found on the prevalence of histamine releasing autoantibodies in recurrent idiopathic AE (7).
The objective of this study was to report the prevalence of positive histamine releasing autoantibodies in a cohort of patients with recurrent idiopathic AE, and evaluate the usefulness of HR-test in this patient group.

Patients and methods

This was a retrospective cohort study of 612 AE patients seen at the Department of Dermatology, Odense University Hos-

pital, in the study period 1995-2013. All patients had been referred for specialized dermatologic evaluation, due to AE with or without urticaria. The study-population was identified by a search in the medical record system, using the International Classification of Disease version 10 (ICD-10) diagnostic codes T78.3 (angioneurotic edema / Quinke oedema / giant urticaria), L50.8 (urticaria, other), L50.8A (chronic urticaria) and L98.9 (disorder of the skin and subcutaneous tissue, unspecified). Patients were included in the cohort if the information in the medical records were in accordance with AE, with or without urticaria. Patients with complement C1 inhibitor deficiency and acquired complement C1 inhibitor deficiency, as well as patients with a history of angiotensin-converting enzyme inhibitor-induced angioedema, were excluded. Only AE patients who had a HR-test performed were included in this study (404 patients). **Figure 1** demonstrates the process of inclusion and exclusion of patients. A consultant dermatologist or a resident reviewed the medical records. Relevant data on demographics, concomitant rash, co-morbidity, co-medication, treatment regimens and efficacy, hospital admissions and outcome were collected, as well as selected laboratory test results.

HR-test was analyzed at RefLab Aps Copenhagen (http://reflab.dk/). According to this laboratory, the threshold for a positive result was > 16.5 % histamine release.

Ethical considerations

This study was approved by the Danish Data Protection Agency (Journal number 2008-38-0035) and the Danish National Board of Health (Journal number S-20140165).

Statistical analysis

Patients with AE with or without urticaria were compared using Fisher's exact test. Difference of proportion test and odds ratio calculations was employed when comparing treatment efficacy. P-values ≤ 0.05 were considered statistically significant. 95% confidence intervals (CI) were reported when appropriate.

Results

The study population comprised 612 patients. HR-test was performed in 404 patients meeting the study's inclusion criteria. The male : female ratio was 0.73, with a mean age of 50.2 years (range 2-85 years). The cohort was almost exclusively Caucasian. The mean follow-up time was 66.4 weeks. Further details are shown in **table I**. In two patients the test results could not be retrieved, and in three patients it was uncertain from the medical record if they also had urticaria. These five patients were excluded (**figure 1**).

The HR-test was positive in 10 out of 231 patients with AE without urticaria (4.3%) and in 29 out of 168 patients with

Figure 1 *- Flow-chart demonstrating the process of selecting patients with positive HR-test.*

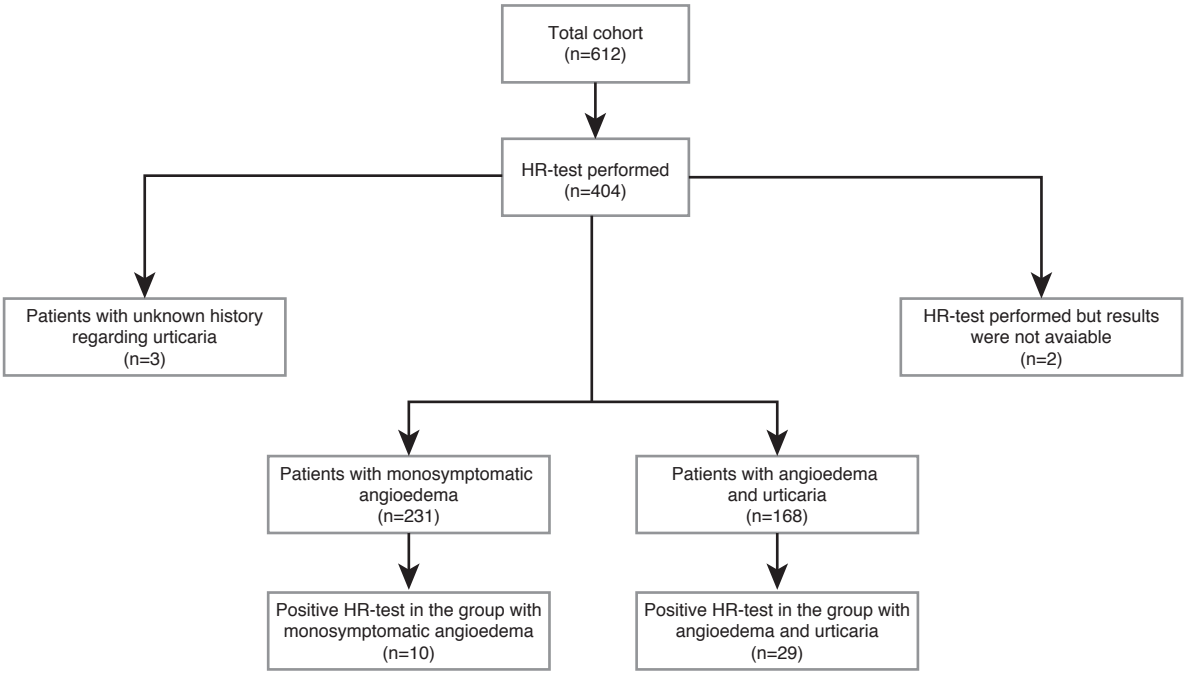

Table I *- Demographic and clinical data of patients with angioedema (AE) +/- urticaria.*

Total number of patients with HR-test performed	404
males	171
females	233
m : f-ratio	0.73
Age, mean, median, [range], years	50.16, 51.39, [range 2.1-85.1 years]
Ethnicity	
Caucasian	393
Middle Eastern	3
Black	1
Asian	5
other	1
Current tobacco use, n	
yes	70
no	188
unknown	146
Number of patients with a positive family history of AE	31
Number of HR-tests, total	404
positive	39 (9.7%)
negative	360 (89.1%)
unknown result	5 (0.5%)
Comorbidities	
diabetes mellitus	32
hypertension	115
ischemic heart disease	24
heart failure	7
atopic dermatitis	21
allergic rhinitis	56
asthma	42
other respiratory disease	4
Follow-up time, mean ; [range], weeks	66.4; [0 - 675 weeks]
Number of reported efficacy of antihistamines	266
Number of reported efficacy of corticosteroids	162
Number of patients hospitalized due to AE	138 (34.2%)
Number of patients with ER visits due to AE	144 (35.6%)

Table II *- Different treatments and their efficacy on angioedema patients +/- urticaria.*

	Medications	**Number of treated individuals**	**Efficacy on angioedema**
positive HR-test and monosymptomatic angioedema (n = 10)	anti-histamines	10	5 (50%)
	corticosteroids	7	4 (92.9%)
	adrenaline	3	2 (66.7%)
negative HR-test and monosymptomatic angioedema (n = 221)	anti-histamines	202	132 (65.3%)
	corticosteroids	134	80 (59.7%)
	adrenaline	34	14 (41.2%)
positive HR-test and angioedema with urticaria (n = 29)	anti-histamines	27	22 (81.5%)
	corticosteroids	20	13 (65%)
	adrenaline	3	1 (33.1%)
negative HR-test and angioedema with urticaria (n = 139)	anti-histamines	135	107 (79.3%)
	corticosteroids	86	65 (75.6%)
	adrenaline	14	5 (35.7%)

AE and urticaria (17.3%) (p = 0.0005, 95% CI 5.64 to 20.14). Among 399 included patients, sufficient treatment data were available in 374 patients. **Table II** shows the different drugs used and their efficacy. When monosymptomatic AE patients with positive HR-test were compared with monosymptomatic AE having a negative HR-test, the odds ratio was 1.9 for a positive effect of antihistamines. This finding was not significant (p = 0.25, 95% CI 0.528 to 6.7352). Comparing the same groups, the odds ratio was 1.1 (p = 0.59, 95% CI 0.2391 to 5.1635) for having a positive effect of corticosteroids.

The treatment efficacy of antihistamines and corticosteroids was also studied among AE patients with concomitant urticaria. The subgroup of patients with positive HR-test was compared with patients having negative HR-test. The odds ratio was 0.86 (p = 0.51, 95% CI 0.302 - 2.498) for having a positive effect of antihistamines, and 1.67 (p = 0.24, 95% CI 0.5878 - 4.7261) for corticosteroids. The treatment response of adrenaline could also not be predicted by HR-test result, as those with monosymptomatic angioedema and positive versus negative HR-test had an odds ratio of 0.71 (p = 0.64, 95% CI 0.0589 - 8.6651). Patients with concomitant urticaria and positive versus negative HR-test had an odds ratio of 1.11 (p = 0.73, 95% CI 0.0795 - 15.5348).

Table III *- HR-test results from studies of patients with urticaria (wheals) and angioedema (AE) also showing cut-off values for HR-test.*

Author	Basophil histamine release test (HR)	Number of patients with monosymptomatic AE	Number of patients with AE with wheals	Number of patients with only wheals	Number of healthy controls	Total positive HR
Iqbal et al. 2012 (3)	> 16.5% cut-off			398 (urticaria with and without AE) 105 positive HR		105
Grattan et al. 1991 (4)	> 10% cut-off			25, 14 positive HR	10, 0 positive HR	14
Hide et al. 1993 (5)	> 10% cut-off			26, 17 positive HR		17
Tedeschi et al. 2012 (7)	5% cut-off	19, 2 positive HR	38, 18 positive HR	52, 11 positive HR	20, 0 positive HR	31 (2 AE, 18 AE with wheals, 11 with wheals)
Grattan et al. 2000 (10)	> 5 % cut-off			27, 14 positive HR		14
Platzer et al. 2005 (11)	> 16.5% cut-off			901, 323 positive HR	9, 0 positive HR	323
Szegedi et al. 2006 (12)	11.6% cut-off for atopic donor serum 7,3% cut-off for non-atopic serum			72, 37 positive atopic donor serum, 23 positive non- atopic donor serum [1]	20, 0 positive HR	60
Zuberbier et al. 2000 (13)	> 10% cut-off			13, 7 positive HR		7
Godse et al. 2010 (14)	> 16.5% cut-off			20, 9 positive HR		9
Hyry et al. 2006 (15)	> 12% cut-off			10, 4 positive HR		4
Sabroe et al. 1999 (16)	≥ 5% cut-off			155, 54 positive HR	40 0 positive HR	54
Kaplan, Joseph. 2007 (17)	≥ 15% cut-off			104, 54 positive HR		54
Perez et al. 2010 (18)	> 16.5% cut-off			6 (where HR test was performed), 2 positive HR with CU, 1 positive with urticarial vasculitis		3
Berti et al. 2017 (19)	> 16.5% cut-off		14	6		9 out of the 20 patients had a positive HR test
This study	> 16.5% cut-off	231, 10 positive HR	168, 29 positive HR			39

[1]Atopic serum leads to a significantly higher histamine release. HR-test performed with blood from two donors.

Discussion

In this retrospective study of 404 patients, we analyzed the frequency of functional histamine releasing autoantibodies in a cohort of patients with AE with or without urticaria. We found a frequency of 4.3% with a positive HR-test in the subgroup of patients with mono-symptomatic AE, and 17.3% with a positive HR-test in the subgroup of patients with AE and urticaria. This makes sense, since the wheal and flare response is most often connected to histamine release, whereas the vasoactive mediators in angioedema are more dubious and may include other mediators such as bradykinin (8).

Comparing patients with mono-symptomatic AE with positive HR-test contra negative HR-test, the odds ratio was 1.9 for having a positive effect of antihistamines. This could be a signal to guide in an individualized therapy, but unfortunately the finding was not significant, possibly due to the number of included patients. In a large clinical survey, it has been shown that most patients (254 of 294) with monosymptomatic AE responded completely or partially to antihistamines, however no data on the HR-test was provided (9).

In the subgroup of AE patients with co-existing urticaria, neither the treatment efficacy of antihistamines, corticosteroids nor adrenaline differed significantly between HR-positive and HR-negative individuals. Unfortunately, we could not retrieve sufficient efficacy data of cyclosporine in this study. It is known from the literature that patients with antihistamine-unresponsive urticaria and a positive HR-test may respond better to cyclosporine than patients with a negative HR-test (3,10). No data on monosymptomatic angioedema, HR-test and treatment response to cyclosporine or other drugs could be found.

Sparse data could be found in the literature on HR-testing in patients with angioedema (7). Only the study by Tedeschi and coworkers investigated HR-testing in monosymptomatic angioedema patients. They divided their cohort into subgroups of patients with AE with or without urticaria, suggesting that a positive HR-test is linked to urticaria and not AE, which could be confirmed in this study. Higher rates of positive HR-tests were found in the literature, possibly explained by a lower cut-off value in the majority of these studies as seen in **Table III** (3-5,7,10-19).

The main limitations of the present study are the retrospective design with data collection from the patients' medical records over a 20-year period. We cannot exclude possible bias in the study, as different colleagues have made the clinical observations and not all symptoms may be listed in the medical records. The HR-test became commercially available in our country in 2004, and has been used routinely in all patients with urticaria seen at our department between 2005 and 2013. A prospective study would be preferable, and should include a valid and reliable measure of disease activity; i.e. the Angioedema Activity Score (20).

We could not compare data with autologous serum or plasma skin tests (ASST and APST), as these are not routinely performed in our country. According to the findings of Berti et al., there does not seem to be any association between in vivo and in vitro tests in patients with CU (19), and the same could be true for AE. The performance of ASST and APST would be desirable to study in the future, to confirm these findings also in mono-symptomatic AE. In conclusion, we cannot see any diagnostic or therapeutic value of HR-test in mono-symptomatic AE.

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Conflicts of interest

Dr. Eva Rye Rasmussen has collaborated with Shire and CSL Behring regarding angioedema research. This study was not directly supported financially. Dr. Rasmussen has received honorariums for lectures at angioedema meetings from Shire and MSD Norway.

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