

ANTI-IgE INDUCED HISTAMINE RELEASE FROM BASOPHILS IN CHILDREN WITH ATOPIC DERMATITIS

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Abstract. Histamine release (HR) induced by anti-IgE (1 to 10 000 ng/ml) from whole-blood basophils has been evaluated in 29 children with atopic dermatitis (AD). HR was found to be reproducible and did not vary with the clinical improvement or aggravation of AD. Children with AD were found to have a higher HR than controls. Two groups of children with AD could be distinguished on the basis of histamine release. These groups did not differ with regard to age, age of onset, clinical severity, or serum IgE levels.

Key words: Histamine release; anti-IgE; Basophils

Histamine release from circulating basophils exposed to anti-IgE is one of the parameters used to test basophil "releasability". It seems likely that "releasability" could be an important factor for the understanding of allergic diseases (4). To our knowledge, "releasability" in infantile atopic dermatitis (AD) has not previously been studied. We have studied HR induced by anti-IgE in 29 children with AD, its spontaneous variability, and its correlation with various parameters.

MATERIAL AND METHODS

The release of histamine from circulating basophils was measured according to Siraganian (6); this technique is carried out with whole blood and not with washed buffy coat cells. Histamine release was assayed according to Shore (5) by means of a continuous flow automated fluorimetric method. The experimental error was $\pm 2\%$ for histamine concentrations in excess of 2 ng/ml and $\pm 5\%$ between 0.1 and 2 ng/ml. The results were linear between 0.1 ng/ml and 5 $\mu\text{g/ml}$. Anti-IgE serum was purchased from Sodalen and used at a concentration of 1, 10, 100, 1 000 and 10 000 ng/ml of anti-IgE antibody. Levels of serum IgE were measured by the immuno enzymatic method (2). This study concerned 29 children with atopic dermatitis (AD), mean age 4.2 years, ranging from 6 months to 14 years, each child being studied at different times. The activity of the disease was scored clinically according to the method of Clendenning (1). 18 normal children without a personal or a family history of atopy were tested as controls.

RESULTS

1. *Spontaneous variability of histamine release in AD.* Tables I and II show that when two HR determinations were performed at an interval of several weeks, in 28 children, only slight variations in HR were seen between the first, second and third determinations. These slight variations in HR were seen although greater (but not significant) variations in serum IgE levels were observed. Furthermore, there was a significant improvement in the clinical state without modification of HR.

2. *HR in AD and in controls.* Table III shows that a higher percentage of HR is induced by 1 000 and 10 000 ng/ml of anti-IgE in AD than in controls. This difference was not observed with the other concentrations of anti-IgE. Total histamine content was higher in AD than in controls.

3. *Subgroups in AD.* Eleven children were found to release less than 25% of the total histamine after

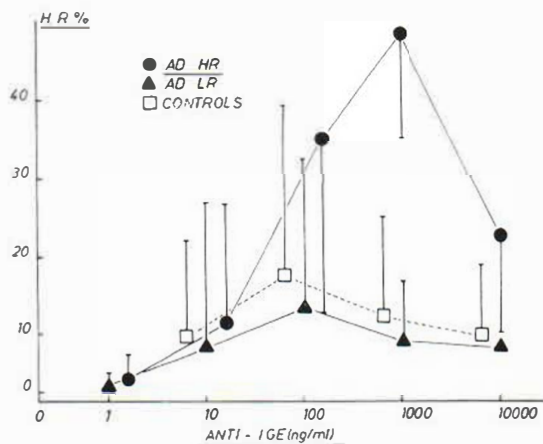


Fig. 1. Histamine release induced by varying doses of anti-IgE in normal children (control) and children with atopic dermatitis. ADHR = atopic dermatitis high responder, ADLR = atopic dermatitis low responder.

Table I. Reproducibility of the histamine release induced by varying doses of anti-IgE

The mean variations ($m\Delta$) between two successive HR determinations in the same child are not significant. Parallel variations of serum IgE are not significant. There is a significant decrease in the clinical score

	Variation of the % HR by anti-IgE				Variation of serum IgE (IU/ml)	Variation of clinical score
	1	10	100	1 000 ng/ml		
$m\Delta$, %	2.2	6.4	9.7	12.5	536	16
\pm	3.36	9.08	9.69	14.05	623.40	13.09
Signif.	N.S.	N.S.	N.S.	N.S.	N.S.	$p < 0.05$
nb	24	28	28	28	16	24

Table II. Variation in histamine release in 10 children with AD

Results of two to three assays at an interval of several weeks. No variations were seen. Low responders remained low responders and high responders remained high responders (see Fig. 1)

Patient	% of histamine release by anti-IgE serum														
	1 ng/ml			10 ng/ml			100 ng/ml			1 000 ng/ml			10 000 ng/ml		
	1st	2nd	3rd	1st	2nd	3rd	1st	2nd	3rd	1st	2nd	3rd	1st	2nd	3rd
Bal.	0	0	—	0	0	—	0	0		0	0.7				
Gay.	0	0	—	0	0	—	0.7	0.7		5	6.3				
Mar.	2	0	—	5	0	3.4	6.1	3.2	4.9	2.5	2	14			3.5
Lar.	0	0		0	0.7		14	16.2		20	14				
Cou.	3	0	0	5	2	3.8	7	2	6.8	26	29	40.6			
Caz.	0	0		0	0		8.5	0.7		56	44				
Fior.	0	0		25.3	43		53.6	55.3		36	31				
Han.	0	1.6	7	40	36	50	82	68	73	79	68	73			
Leg.	7.6	1.9	15.3	15	5.4	20.8	35.5	23.0	21.5	58.9	63.2	63.6			
Pedr.				65.4	70.6		70.6	63.2		16.1	8.0		7.6	3.3	

Table III. Histamine release in AD and controls

The percentage of histamine release was significantly higher in children with atopic dermatitis than in controls

	Atopic dermatitis 79.9 \pm 31.5					Controls 56.9 \pm 23.8				
	1	10	100	1 000	10 000	10	100	1 000	10 000	
Total histamine content ...										
Anti-IgE, ng/ml ...										
Histamine release, %										
Mean	0.7	10.2	26.4	32.0*	19.2*	8.7	17.3	12.2*	8.3*	
σ	1.6	16.7	24.1	22.2	12.3	14.4	22.0	15.7	10.7	
Number of tests	24	29	29	29	5	18	18	18	18	

* U: Mann and Whitney, $p < 0.01$ for 1 000 and $p < 0.05$ for 10 000 ng/ml. Total histamine content was higher in AD than in controls $p < 0.01$.

exposure to 1 000 ng/ml anti-IgE (7.16 ± 7.08). Eighteen were found to release more than 25% (47.8 ± 12.05). Total histamine content was similar in both groups (70.5 ± 27 and 85.5 ± 33). No differences in age, age at onset, clinical severity or total serum IgE levels were found between the two subgroups.

DISCUSSION

Two facts emerged from this study. 1) HR by anti-IgE is quite constant in a given child with AD. Such a reproducibility has previously been shown for HR in urticaria (3). There were no great variations between two HR determinations although the clinical state varied dramatically in some children. Therefore, it appears that HR is not correlated with the severity of the disease. 2) On the basis of HR induced by 1 000 ng/ml of anti-IgE it was possible to distinguish two subgroups in children with AD. One had a low response which was quite similar to that of controls. The other had a high response even though the total histamine content was no different from that of the low responder group.

Efforts at subgrouping AD seem important, for instance in the evaluation of the prognosis. We have found that the low responder group did not differ from the high responder group with regard to age, age at onset, clinical severity of the disease, or serum IgE; unlike most of these parameters "releasability" may prove to be an interesting parameter in the evaluation of children with AD. Finally, the theoretical meaning of these findings has to be evaluated, keeping in mind that the technique is performed with whole blood.

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DISCUSSION

Rorsman (Lund). Q: You could in some way relate the difference in the histamine release by your anti-IgE to your IgE level in serum. You need a minimum number of IgE molecules on your basophils to get histamine release. Do you think you did not have enough IgE molecules when you did not obtain histamine release?

A: A little boy who was tested at monthly intervals had a significant variation in serum IgE between 1 000 and 2 000 units, but the releasability was not different. This is a point we cannot explain.

Zachariae (Aarhus). Q: We measured daily urinary excretion of histamine in very severe atopics with high IgE levels and we found only 1/10 with an increased excretion. This is completely different from what we found in urticaria and angioedema patients where we found high urinary excretions. I do not want to rule out histamine as a very important agent in atopic dermatitis, but we cannot use it as a parameter.

A: If you look for total histamine in urine you have the 24-hour metabolism. It is impossible that histamine would inhibit chemotaxis, since plasma levels of histamine are so low there. However, in a cell-to-cell contact you may have an increased concentration.

Hanifin (Portland): It has been shown by several workers that the tissue histamine levels are elevated. When we did histamine inhibition of chemotaxis we found very narrow tolerances; molarities of 10^{-4} did not inhibit chemotaxis that 10^{-6} inhibited. So there is a very peculiar relationship there. I think you will have to collect the urine in the middle of the night when they start the flare.