

Heterozygous α_1 -antichymotrypsin deficiency may be associated with cold urticaria

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Proteins of the serpin family (serine protease inhibitor) control key steps in the inflammatory, coagulation and complement systems. C₁-inhibitor deficiency predisposes to hereditary angioneurotic oedema, and other serpins control proteolytic enzymes that may cause complement activation or the forming of oedema. We investigated whether deficiency of proteins of the serpin family may predispose to cold urticaria and therefore screened 7 male patients with severe cold urticaria for the presence of deficiency alleles of some of the members of the serpin antiprotease family. There were no findings of C₁-inhibitor, α_1 -antitrypsin, α_2 -antiplasmin, antithrombin III, tissue plasminogen activator inhibitor or thyroxine binding protein deficiency. The prevalence of heterozygous α_1 -antichymotrypsin deficiency was significantly higher than expected (prevalence ratio 25.8 (95% confidence interval 6.0–112), $p < 0.0001$). This finding is in concert with previous studies that have shown lower mean levels of α_1 -antichymotrypsin among patients with cold urticaria and suggests that heterozygous deficiency of this antiprotease, which controls neutrophil cathepsin G and mast cell chymase may predispose to cold urticaria. The present series is, however, small and the results need confirmation in larger materials.

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The serpin family (serine protease inhibitor) originates from a common ancestral gene and contains single chain proteins of similar molecular mass, homologous in amino acid sequence and in some instances in gene arrangement and function (1, 20). Some of the members of this family have been implicated in dermal affections, e.g. C1-inhibitor in hereditary angioedema (10) and piZ α_1 -antitrypsin in psoriasis (3) and panniculitis (6), while other serpins (α_1 -antichymotrypsin (ACT), antithrombin III, α_2 -antiplasmin, tissue plasminogen activator inhibitor, protein C inhibitor, thyroxine binding globulin, cortisone binding globulin) have not.

Two reports have shown decreased plasma concentrations of α_1 -antichymotrypsin in cold urticaria (4, 9). However, there were no analyses as to heredity or other putative causes for the lower plasma ACT.

We have described an hereditary deficiency of ACT (11). In heterozygous α_1 -antichymotrypsin deficiency the plasma concentrations are approximately half of the normal mean, and the trait (the heterozygote frequency in Sweden is 0.6%) is associated with childhood asthma (12, 14), food allergy (14) and subclinical emphysema (13).

To test whether serpin deficiencies predispose to cold urticaria 7 male patients with severe cold urticaria were screened for subnormal plasma concentrations of α_1 -antitrypsin, α_1 -antichymotrypsin, antithrombin III, α_2 -antiplasmin, tissue plasminogen activator inhibitor, thyroxine binding globulin and C1-inhibitor. The results suggest an association between heterozygous ACT deficiency and cold urticaria.

Material and methods

Seven male patients with severe recurrent cold urticaria who attended the outpatient clinic at the Department of Dermatology were included, primarily for an experiment with cold provocation to measure histamine levels. No previous measurements of proteins belonging to the serpin family had been done among these patients.

Blood samples (K₃-EDTA, final concentration 3.8 mmol/l spun at room temperature at 1000 $\times$ g for 15 min) were drawn in the fasting state from the antecubital vein before cold provocation and stored at -20°C until analysis. All 7 subjects responded in a typical manner to cold provocation.

α_1 -Antichymotrypsin, α_1 -antitrypsin concentrations and Pi-typing were done as previously described (13), measurements of antithrombin III, α_2 -antiplasmin, tissue plasminogen activator inhibitor were done at the Department for Coagulation Disorders at the hospital, thyroxine binding globulin at the Department of Clinical Chemistry at the Malmö General Hospital and C1-inhibitor at the Department of Medical Microbiology, Lund Hospital. All samples were analysed using standard methods for the hospitals involved.

We used the prevalence rate ratio to calculate the relative risk for cold urticaria in heterozygous ACT deficiency (13). The prevalence rate was taken from our population screening where 12 women of 1872 were classified as ACT deficiency heterozygotes (13).

Results

The results are summarized in Table 1. The levels of C1-inhibitor, α_1 -antitrypsin, α_2 -antiplasmin, thyroxine binding globulin and antithrombin III were normal or slightly raised in all patients. One patient had the PiMS and another the PiFM α_1 -antitrypsin phenotype. The tissue plasminogen activator inhibitor activity was within the normal range in all patients.

One patient had subnormal plasma ACT concentration which he shared with his mother, who had a plasma concentration of 63% (i.e. he may be a heterozygote for α_1 -antichymotrypsin deficiency). The prevalence ratio (1/6 vs 12/1860) was 25.8 (95% confidence interval 6.0–112), $p < 0.0001$. Challenge with an ice cube did not influence the plasma ACT concentrations.

Discussion

The main finding of the present study is that the prevalence rate ratio of heterozygous ACT deficiency was several times higher than expected (25.8 (95% confidence interval 6.0–112). Basing this solely on the presence of one case among 7 patients with cold

urticaria may seem unjustified, but if we take into consideration the extremely low probability of this finding, from a theoretical point of view, common sense suggests that this was not merely a coincidence. The finding is in accord with previous reports showing decreased plasma concentrations of ACT among patients with cold urticaria (4, 9). The lower mean plasma concentrations in this group of patients may indicate an increased prevalence of heterozygous ACT deficiency.

ACT controls the activity of neutrophil cathepsin G and mast cell chymase (2). Both are serine proteases and have ACE-activity (angiotensin converting enzyme) and inactivate bradykinin, thus producing vasoconstriction (18, 19).

Further, chymase cleaves both VIP and substance P (8). It has been claimed that in human skin, chymase release from substance P-stimulated mast cells is highly likely to terminate or attenuate axon reflex-mediated neurogenic inflammation by cleaving substance P and calcitonin gene-related peptide (5). Cathepsin G is active on endothelium (15), and cleaves fibronectin, laminin, elastase and activates neutrophil collagenase (7, 16, 17, 22). Mast cell chymase has recently been shown to potentiate histamine-induced wheal formation in ragweed-allergic dogs (21). Chymase alone did not cause wheal formation but increased the wheal size after histamine administration. A tenable hypothesis is that insufficient control of cathepsin G or mast cell chymase may lead to downstream vasoconstriction and increased permeability at the site of mast cell degranulation with oedema, degradation of connective tissue elements and inflammation in the surrounding tissue.

Heterozygous ACT deficiency may only explain a part of cold urticaria and it is probably not the sole explanation even in ACT deficiency heterozygotes. Other factors that may predispose to cold urticaria are complement factor abnormalities or increased levels of neuropeptides (23).

The present study shows that deficiencies of ser-

Table 1.

Pat. #	ACT (68–133%)	AAT (0.9–1.7 g/l)	C1-inh. (72–153%)	ATIII (0.8–1.1 IE/ml)	α_2 -PI (70–115%)	tPAI (0–21 IE/ml)	TBG (10–23 mg/l)
1	75	1.09	82	1.27	110	3	18
2	93	1.65	99	1.14	100	1	30
3	90	0.97	79	1.31	94	14	23
4	63	1.00	114	1.23	99	4	21
5	93	1.26	74	1.11	107	3	29
6	115	1.47	103	1.43	106	0	28
7	98	1.07	75	1.22	121	M	26

Abbreviations: ACT: α_1 -antichymotrypsin, AAT: α_1 -antitrypsin, C1-inh.: C1-inhibitor, ATIII: antithrombin III, α_2 -PI: α_2 -antiplasmin, tPAI: tissue plasminogen activator inhibitor type 1, TBG: thyroxine binding globulin. Normal range within brackets.

pins other than ACT are uncommon phenomena in patients with cold urticaria. The present methods do not, however, allow detection of all possible forms of phenotype abnormality, and we cannot thus exclude that some of these 7 patients may have such.

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