Adrenergic Urticaria and Adrenergic Pruritus

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We report here on 2 patients with adrenergic urticaria and adrenergic pruritus, respectively. The lesions and features developed during phases of stress and during the attacks were associated with an increase in the plasma concentrations of noradrenalin, adrenalin and prolactin. The dopamine plasma level was elevated only in the case of adrenergic urticaria. The symptoms could be reproduced by intradermal injection of adrenalin and noradrenalin and treated successfully with propanolol, a blocker of β-adrenergic receptors. Adrenergic urticaria is a rare but distinct entity, which has to be separated from cholinergic urticaria. Adrenergic pruritus seems to be a minor variant of adrenergic urticaria. ***Key words: Noradrenalin; Adrenalin; Cholinergic urticaria.***

(Accepted June 7, 1989.)

Acta Derm Venereol (Stockh) 1990; 70: 82–84.

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Eliciting factors of most types of physical urticaria are well-defined (1). In 1985, Shelley & Shelley (2) de-

scribed a new entity of stress- and emotion-related urticaria, which is triggered by noradrenalin and adrenalin and which has to be differentiated from the cholinergic urticaria. Both forms of urticaria are mediated by neurotransmitters (3). Here we report on 2 cases: one with urticaria and one with pruritus. Adrenergic pruritus has to the best of our knowledge not been studied before.

CASE REPORTS

Case 1

A 51-year-old manager of a big company has suffered from urticarial attacks for 2 years, especially at times of negative stress, when he could not cope with the problems faced and the decisions to be made. The attacks occurred more and more frequently, with free intervals during weekends and holidays and during a stay at a sanatorium. He has been examined by a clinical psychologist who diagnosed a high psycholability and the need for psychotherapeutic intervention, with hypnosis and autogenous training. The urticaria appeared as generalized lesions, partly macules of 3–5 mm in diameter, partly papules of 1–4 mm in diameter, sometimes with a white halo of 3–5 mm. Dermographism was within the normal range. Coffee provoked an attack on several occasions within 30 to 60 min and so did the acute emotional stress. Clemastin 2 mg or Ketotifen (Zaditen) 2 mg provided alleviation during the attacks. Neither physical exercise nor hot baths were able to provoke the urticaria.

Studies on the clinical examinations and routine laboratory methods performed before and during attacks did not reveal any abnormalities, including blood pressure, cryoglobulins, plasma histamine and serotonin. Serum IgE was increased (2.9 mg/l, normal 0.07–1.8 mg/l). Blood samples for catecholamines were taken with special care (horizontal position of the patient under resting conditions, remaining tubule, cooled heparinized plastic syringes, addition of antioxidants to the plasma). Adrenalin concentrations in plasma decreased from 8.05 and 9.29 nmol/l during two different attacks to 1.12 and 1.04 nmol/l in the symptom-free intervals (normal 0.1–1.0 nmol/l) as determined by high-pressure liquid chromatography. The same applied to noradrenalin, which decreased from 8.8 and 9.8 nmol/l to 1.15 and 2.96 nmol/l (normal 1.2–3.4 nmol/l). Dopamine decreased from 15.6 and 5.7 nmol/l to 1.16 and 1.39 nmol/l (normal 0.05–0.6 nmol/l). In addition prolactin was increased (800 mE/l, normal 30–500 mE/l) during attacks, whereas it was normal in two other symptom-free intervals (400 mE/l, 450 mE/l).

The hives could be reproduced by intracutaneous testing with adrenalin (about 10 ng in 0.02 ml saline) and noradrenalin (about 5 ng), resulting in flares between 2 and 5 mm in diameter, surrounded by a white halo of 1 to 4 mm. The increase in the dosage led to vasoconstriction (blanching phenomenon). Control persons, patients with chronic idiopathic urticaria as well as with other forms of physical urticaria did not show any hives after injections of adrenalin and noradrenalin. Histamine and serotonin exhibited normal skin reactivity as compared with the controls. In addition, the patient had negative skin reactions to acetyl β-methylcholine chloride (5.1×10^{-4}, 5.1×10^{-5} mol/l) and nicotine acid tartrate (2×10^{-7} mol/l).

The local intracutaneous administration of 2 ml of atropine sulfate (total dosis 0.05 mg), propanolol hydrochloride (total dosis 0.1 mg) and tolazoline hydrochloride (total dosis 1 mg) into an area measuring 5×5 cm gave the following results. The development of hives could be blocked by propanol and by tolazoline in an area of about 8×8 cm, but not by atropine.

In the skin biopsy of a hive, only edema and a few inflammatory cells could be found. By using the blocker of the β-adrenergic receptors propanolol (Obsidan®, VEB Isis-Chemie, Zwickau, GDR, 25 mg three times a day) the urticaria could be suppressed. However, it reappeared after discontinuing this therapy.

Case 2

A 34-year-old woman has suffered from episodic pruritus after emotional stress for 3 years. Wheal and flare reactions have never been observed. The pruritus developed within 60 min and lasted for about 2 to 3 h in a more or less generalized form. The patient was mother of three children and was employed with the local council as a clerk. She was altogether overstrained with her job and housework, when her husband, who worked in a leading position, claimed neglect by his wife, who exhibited some stigmata of psycholability. The results of laboratory routines were within normal limits. Serum IgE was increased (2.6 mg/l). Plasma histamine, serotonin and dopamine were normal, while adrenalin and noradrenalin were elevated during an attack (4.27 nmol/l, and 4.68 nmol/l, respectively) versus normal levels in the interval (1.14 nmol/l and 1.18 nmol/l, respectively). Prolactin levels in serum were increased on three occasions (900, 750, 800 mE/l; attack and 2 intervals).

Local itching could be reproduced by intradermal testing with adrenalin and noradrenalin and could be blocked by local administration of propanolol and tolazoline, but not by atropine. The other tests as described in case 1 gave no positive reactions. Moreover, the exposure with water at various temperatures did not provoke any pruritus. Improvement of the pruritic attacks could be achieved by application of propanolol (Obsidan®, 25 mg twice a day).

DISCUSSION

In the adrenergic urticaria, tiny papules are surrounded by a small blanched halo due to vasoconstriction. In the cholinergic form similar papules are located in the centre of a large erythematous flare caused by vasodilatation.

Increases in the plasma levels of noradrenalin, adrenalin, dopamine and prolactin are crucial diagnostic features for adrenergic urticaria. However, it must be taken into consideration that levels of catecholamines are variable and can be provoked by exogenous and endogenous factors and can change very rapidly. During the circadian rhythm, maximum values of noradrenalin and adrenalin did not exceed the normal range by factors exceeding 1.8 (4). (Sub)maximal provokation during graded cycle ergometer exercise exhibited differing results for noradrenalin and

adrenalin: no significant increases in healthy persons and decreases by one-third in well-trained athletes (5), on the other hand, increases by factor 10 for noradrenalin and factor 17 for adrenalin in healthy persons (6). In addition, there are several published reports concerning the relations to the sympathetic nervous system: increases in noradrenalin levels under orthostatic conditions by factors 3 (7), after cold pressure test by factor 1.4 (8) and after valsalva-test by factor 2 (9). Finally, we could not find any reports on values in otherwise normal individuals who are known to be chronically over-anxious, emotionally labile and unable to cope with persistently stressful situations. It is conceivable that values seldom return to normal in these patients. In our patients we found increases in noradrenalin and adrenalin levels by factors between 9 and 4 and for dopamine between 13 and 4 under resting conditions. Moreover, increased plasma prolactin levels have been described during phases of stress.

Intracutaneous tests with nor-/adrenalin and acetylcholine, respect., can reproduce each type in a specific way and serve as an important diagnostic tool. Tests must be performed with weak dilutions of acetylcholine (0.02 ml of 10^{-3} to 10^{-5}) (10) and noradrenalin (0.02 ml of 0.5×10^{-6}) (11). In our first patient the cholinergic urticaria could be excluded by specific tests as described by Commens & Greaves (3). In our second patient we observed only a pruritic reaction as a minor expression of the same pathogenetic mechanism. An aquagenic pruritus could be excluded by anamnesis and exposure to water (12). The Local application of the anticholinergic agent atropine did not prevent the development of lesions and features. However, the β- and α-adrenergic blocking agents propanolol and tolaznline were able to block the pathogenesis in both patients. Concerning therapy, one has to consider non-specific sedation of the autonomous nervous system by tranquillizers and ataractica and the blocking of H_1 receptors by antihistaminica. Histamine seems to be involved as the ultimate step in the pathogenesis of adrenergic urticaria, since Shelley & Shelley (2) have shown mast cell degranulation in electronmicroscopic studies of their patients.

Specific therapeutic effects could be achieved by blockers of the β-adrenergic receptors, such as propanolol, in both of our patients. An ataractic effect of propanolol may additionally contribute to this result. Normally, mast cells express receptors for IgE and for adrenergic substances (13). IgE levels were increased. It is not known whether in this type of urticaria the number of adrenergic receptors on mast cells is increased, or the threshold of activation is lowered, or whether noradrenalin exerts its activity in connection with an antigen or with a serum factor (immunoglobulin) as shown in cholinergic urticaria (11, 14).

ACKNOWLEDGEMENTS

We express our gratitude to Prof. Dr Helga Marek and Dr G. Scholz, Division of Endocrinology, Dept. of Internal Medicine, Karl Marx University Leipzig, for the determination of noradrenalin, adrenalin and dopamine levels and helpful advice.

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