

FAMILIAL LOCALIZED HEAT URTICARIA OF DELAYED TYPE

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Abstract. A hitherto unknown type of heat urticaria is described. The disorder is familial with symptoms since childhood and is characterized by localized, sharply marginated wheals appearing $1\frac{1}{2}$ to 2 hours after heat exposure. There is no immediate whealing. The urticarial reaction reaches its maximum 4 to 6 hours after heat exposure and may persist for 12 to 14 hours. The urticarial reaction to heat is completely inhibited by pretreatment both with a local anesthetic and compound 48/80. It is diminished by atropine and by oral treatment with antihistamines as well as by repeated heat challenges of the same area with 24-hour intervals. The cutaneous reactions to kallikrein, bradykinin, prostaglandin E and metacholine are normal. Histamine and compound 48/80 induce an unusually widespread axon-reflex-mediated flare. A high percentage of the circulating basophils are degranulated. Biopsies from the wheals reveal an inflammatory reaction which is more pronounced than in acute urticaria. The mechanism behind this familial, localized heat urticaria of delayed type is obscure. It seems likely that several mediators are involved. An acetylcholine release might be the primary step which probably starts a chain of reactions including histamine release and possibly an activation of the kallikrein-kinin system.

Localized heat urticaria is characterized by a wheal appearing at the site of application of heat. Only a few clear-cut cases have been described. Lewis (11) and Hopkins et al. (4) had 1 patient with localized heat urticaria which developed within 5 min of exposure to warm water (51°C) and reached its maximum after 3 min. Another patient with the same type of heat sensitivity was reported by Lehner & Rajka (10). A short description of the clinical picture in localized heat urticaria has been given by Baer & Harber (1). A more detailed report has recently been published by Delorme (2) about a patient who developed an erythematous and urticarial plaque sharply localized to the contact area after contact with

anything warm and with the wheal appearing within 5 min after exposure.

This paper deals with a hitherto unknown type of heat urticaria which has been present in a family for three generations. The disorder is characterized by localized, delayed whealing which appears about 2 hours after exposure to heat. The clinical picture will be described as well as studies on cutaneous reactions to various vasoactive substances, basophil degranulation and the Prausnitz-Küstner test.

CASE REPORT

The patient investigated is a 48-year-old female engineer suffering from heat hypersensitivity since childhood. She is otherwise healthy and has not had any relevant, previous illnesses or other allergic symptoms. Her mother, one of her two sisters, two of her three children and four of her deceased sister's five children have the same urticarial response to heat (Fig. 1). The patient, as well as her relatives, first noticed sensitivity to heat in late childhood. It has since then been of the same intensity and did not change during three pregnancies. The symptoms consist of localized urticarial wheals developing on skin areas exposed to heat either through direct contact with a warm object, e.g. radiators or hot water bottles or through radiant heat such as an open fire. Sunbathing with pronounced heating of the skin can also produce wheals, especially on areas covered with dark clothing. Sunlight itself is tolerated well and, if water is sprinkled over the skin while sunbathing, whealing does not occur. A sauna bath for a few minutes provokes whealing, first appearing on skin areas in contact with the wooden benches. During her hospitalization she developed red, sharply limited, urticarial areas on the backs of her thighs 2 hours after leaning on a warm radiator with her clothes on. Use of a hair dryer induces a severe urticarial reaction of the scalp, sometimes with constitutional symptoms as nausea and fever. Physical exercise, sweating, warm baths (37°-39°) or mental stress do not produce any urticarial symptoms.

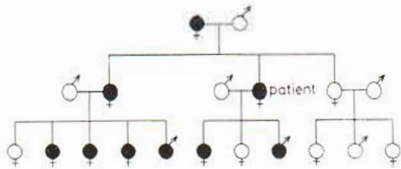


Fig. 1. Pedigree on familial localized heat urticaria of delayed type. Black symbols indicate family members with manifest heat hypersensitivity.

The urticarial reaction is always of a delayed type developing 1 to 2 hours after exposure to heat. Initially only a slight redness can be seen. After 1 to 1½ hours wheals begin to form and usually after 2 hours maximal size is reached. Development of wheals is accompanied by a burning and pruritic sensation. No tenderness or hyperalgesia has been observed. The urticarial reaction usually disappears in the next few hours, but sometimes persists for 6 to 10 hours. The whealing is always restricted to skin previously heated and it generally consists of a homogenous, turgid, tense, red and moderately elevated area. No generalized urticaria of the common acute or cholinergic type has been observed.

Complete physical examination revealed no abnormalities. She had an immediate type dermatographism, but no delayed type.

Except for a basopenia, laboratory studies revealed nothing abnormal. Liver function tests, urinary porphyrins, serum iron and total iron-binding capacity, plasma electrophoresis and levels of immunoglobulins, including IgE, were all within normal limits. Blood group A, Rh negative. No cryoglobulins, cold agglutinins or antinuclear factors were found. She had normal serum levels of C-1 esterase inhibitor, C-4 and total complement. An intradermal test with the 40 most common allergens revealed a positive reaction for rape-pollen, but was otherwise negative.

The patient's two heat-sensitive children have also been studied and their heat sensitivity confirmed by testing. In one of them, a certain tenderness of the wheals was observed at the time of maximal reaction.

SPECIAL INVESTIGATIONS

Heat. Cylindrical aluminium jars (30 mm diameter) filled with sand kept at 45° were used to test the sensitivity to heat. They were placed on the skin of the back for 0.5, 1, 2.5, 5, 15, and 20 min. The skin surface temperature was 32.5° before testing, during and immediately after it was about 45° and 34° respectively, regardless of the length of the testing period. After removal of the jars, an erythema was seen for about 10 min on the areas exposed to heat for the 5, 15 and 20 min periods. No immediate reaction was seen on the other test areas. The skin appeared normal for 1½ hours. Then an urticarial reaction was observed on the areas exposed to heat for 5, 15 and 20 min. It was first visible at the margins of the heated area and 2 hours later the whole area was elevated, tense, erythematous, sharply marginated

without any signs of a surrounding flare of axon-reflex type (Fig. 2). Independent of localization and time of heat exposure, the wheals were of maximal size 2 to 4 hours after heat exposure and then persisted for 6 to 8 hours and sometimes even up to 14 hours.

With a heat exposure of 5 min, the lowest temperature which could produce an urticarial reaction on the skin of the back was about 43°. If the test jar had a temperature of 40° or lower no whealing occurred.

Different areas on the skin of the back seemed to show about the same sensitivity. There were, however, certain differences between the heat sensitivity of various parts of the body. Thus the skin on the dorsal side of the thighs required longer exposure to heat than did the skin of the back to give an urticarial response.

An urticarial reaction was also observed after a 4-min test exposure to an infra red lamp (Luma 250 W) placed 20 cm from the lateral side of the upper arm. The approximate temperature at skin level was 43°C.

A 10-min hand bath, maintained at 40° produced no reaction.

Rechallenge with heat. If the test areas were exposed to heat (45°) for 5, 15, and 20 min a second time 24 hours after the first heat test, the reactions were diminished. In the 5-min test area only a slight erythema without whealing was seen. In the 15- and 20 min areas only discrete whealing at the margins of the test areas were produced. When the tests were again repeated in the same areas and with the same testing times after 48 and 72 hours, erythema or whealing did not appear in any of the test areas.

Biopsy specimens. Biopsies were taken from normal skin and from an area with a 3-hour-old urticarial wheal. Freeze-dry sections were stained with toluidine blue pH 5.2. In the control biopsy, the number and appearance

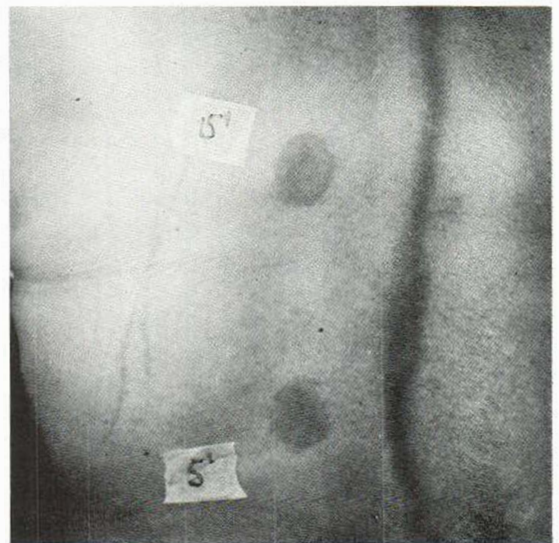


Fig. 2. Localized urticarial wheals; response to heat exposure 2 hours earlier. No immediate reaction; whealing begins 1½ hours after heat test.

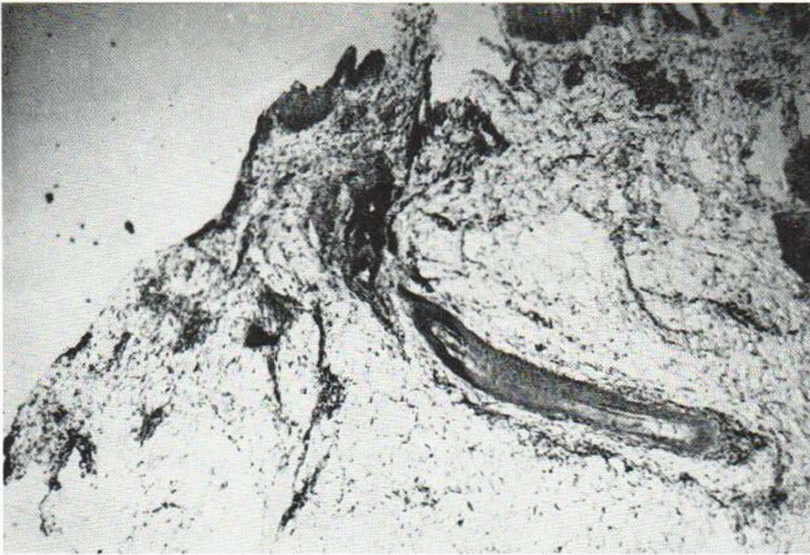


Fig. 3. Biopsy from a 3-hour-old urticaria wheal. $\times 63$.

of the mast cells seemed to be normal as was the amount of other cellular components. The histology of the urticarial lesion differed markedly from that of the control, showing a picture with edema, vasodilatation and numerous areas with pronounced inflammatory cell infiltration in the upper dermis and around the hair follicles (Fig. 3). A few mast cells, all degranulated, were observed.

Light. A light test with wave lengths 2 900–3 300 Å, 3 300–3 800 Å and 4 000–5 000 Å was negative with no abnormal reactions.

Reactions to vasoactive drugs. Histamine 0.01 mg intradermally induced an unusually large wheal and flare. The wheal measured 17 \times 27 mm and the axon-reflex mediated flare 60 \times 120 mm which means a considerably increased reaction compared to that found in healthy controls (8).

The histamine-releasing compound 48/80 (kindly supplied by AB Leo, Hälsingborg, Sweden), 0.01 mg injected intradermally, induced a wheal and flare reaction of about the same size as that of histamine.

The reaction to i.d. kallikrein (Padutin, Bayer AG), 4U, was normal both 20 min and 2 to 5 hours after the injection. A normal response with no signs of delayed whealing was also seen after i.d. injection of bradykinin, 0.01 mg, prostaglandin E₁, 5, 1, 0.5, 0.1 μ g, and metacholine, 0.1 and 0.02 mg, all injected in a volume of 0.1 ml. The reaction to nitrofurfurylnicotinate ointment (Trafuril) was not more erythematous, edematous or persistent than in control subjects.

Sweat. Staining of the sweat pores with *o*-phthaldialdehyde (OPT) (9) was done on a heat-exposed and a control area. No decisive difference in the number of visible sweat pores was observed. Metacholine intradermally appeared to induce a normal sweating response.

Effect of various pharmacologic agents on heat response. The influence of compound 48/80, lidocaine, epinephrine, atropine and an antihistamine on the whealing reaction to heat (45° for 5 min) was tested. A complete inhibition

of the urticarial response to heat was obtained in a skin area injected with compound 48/80, 0.1 mg, 24 hours before the heat exposure.

Infiltration of the skin with 1 ml of 1% lidocaine 15 min before heating also completely inhibited whealing. A symmetrically localized control area showed pronounced urticarial reaction (Fig. 4).

The whealing was slightly reduced in an area where atropine, 0.125 mg in 1 ml of saline, had been injected deeply intradermally 15 min before a heat test.

Antihistamines given orally lessened the urticarial response. Thus, when meclastin (Tavegil, Sandoz), 2 mg, had been given 2 1/2 hours before heat exposure, the resulting urticarial reaction was considerably diminished

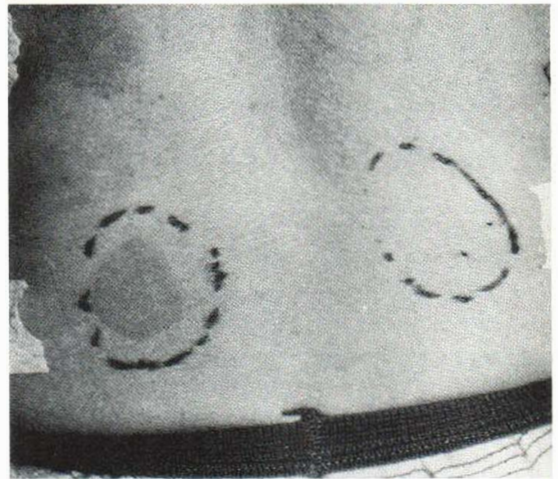


Fig. 4. Inhibition of urticarial reaction to heat by pretreatment with lidocaine (right), control area (left) positive reaction.

Table 1. Percentage of degranulated basophils in blood specimens exposed for a 10-min period to different temperatures

	24°	40°	50°
Control GM	15	9	0
Control CW	10	17	10
Patient	42	48	69

compared with the response without previous antihistamines.

Heat sensitivity of basophils. In order to study whether the heat sensitivity of the basophils in the patient differed from that of healthy controls, the following tests were performed: two hours after a light breakfast, venous blood from the patient and two healthy controls was drawn into heparinized plastic syringes. Samples from each subject were exposed to temperatures of 40° and 50° for a period of 10 min. Control specimens were left at room temperature. A specimen for basophil count was taken at these times and processed by the method described by Shelley & Juhlin (14). The total count of basophils found in the samples from the same individual did not differ markedly with time or temperature. At least 20 consecutive basophils were counted and classified into two groups—degranulated or not degranulated. The percentage of degranulated cells was considerably greater in all the patient specimens than in the controls and in the heated specimens 69% of the basophils were degranulated (Table 1).

Prausnitz-Küstner test. Sera, 0.1 ml from the patient and from a healthy control were injected intradermally into the back of a normal subject 1 hour after the specimens of blood had been obtained. Twenty-four hours later the injected areas were tested for heat sensitivity (45°) for 20 min as described previously. No urticarial response was produced in the following 5 hours.

Patient and control serum specimens kept at approximately 50° for 20 min and then injected intradermally (0.1 ml) induced no urticarial reaction in the following 5 hours either in the patient or in a control subject.

DISCUSSION

Localized heat urticaria seems to be rare. Illig & Kunick (6) in their recent comprehensive review on physical urticaria found few and conflicting reports on localized heat urticaria. Some patients described as suffering from this type of urticaria probably have had a cholinergic urticaria. However, the description on localized heat urticaria given by Baer & Harber (1) and one recently by Delorme (2) seem to make the existence of such a disorder clear. It is characterized by an urticarial reaction appearing a few minutes after contact

with heat and with the wheals sharply limited to the contact area.

We have described here a hitherto unknown type of localized heat urticaria of delayed type. It is familial with onset of symptoms in childhood; the sensitivity to heat seems to be inherited as a dominant genetic factor affecting both sexes. The only previous report on a possible delayed, local urticarial reaction to heat is that given by Duke (3). He had 1 patient with urticaria ab igne with a delayed response to heat like our patient. She, however, required a burn (50°–90°) to develop a whealing reaction, whereas moderate heat exposure produced no reaction. Her family history was negative. It is therefore likely that she had a different type of heat sensitivity.

The clinical picture and the type of heat urticaria in our patient has much in common with the findings in Delorme's patient, but there are also important differences. In both cases the urticarial reaction is sharply limited and localized to the contact area with no pseudopods and no axon-reflex-induced erythema. In both types, repeated heat exposures of the same site will produce a decreased urticarial reaction. The patient described by Delorme had, however, a negative family history and she had no urticarial symptoms before 23 years of age. She then became aware of the abnormal heat sensitivity a few minutes after a warm bath which suddenly induced a systemic reaction. Thereafter, contact with anything warm induced an urticarial reaction within a few minutes. Thus, the reactivity to heat in that patient differs from the type seen in our patient who never has any immediate reactions upon heat exposure. The existence of two types of localized heat urticaria, one of immediate and one of delayed type, thus seems to be conceivable.

The neural, vascular and mediator events occurring in normal skin which has been warmed or heated are not known in detail. When discussing the obscure mechanism behind the delayed whealing after heat exposure, the following findings may be of special interest: a decreased response to heat on repeated exposures, no whealing response in skin areas pretreated with the histamine-releasing compound 48/80 or with a local anesthetic and a certain decrease after pretreatment with atropine. The pronounced axon-reflex-mediated flare reaction to histamine and compound 48/80 might be relevant. The high per-

centage of degranulated basophils may also be noteworthy. The influence of the pharmacologic agents on the whealing reaction is similar to the findings in cholinergic urticaria. A positive Prausnitz-Küstner test was there partially or completely blocked by pretreatment with compound 48/80, by local anesthesia and by atropine (5). An allergic reaction to acetylcholine in that disorder has been postulated by Illig & Heinecke (5).

Acetylcholine is considered as one of the main erythema-producing mediators of the axon-reflex flare (12). This flare is normally blocked by local anesthesia. In our patient an unusually large erythematous flare was seen after intradermal injection of both histamine and compound 48/80 which might indicate a tendency to an increased release of acetylcholine. It might also be speculated that some type of allergic reaction to acetylcholine is possible in localized heat urticaria as well as in cholinergic urticaria. Acetylcholine might then act as a hapten which binds some local substance to form an antigen or it might activate a tissue factor which might in itself act as an antigen. Another possibility is that acetylcholine and heat together could induce the formation of some tissue factor which directly or indirectly will cause a subsequent wheal formation. Such a process need not necessarily have any allergic background. The absence of visible whealing after 5 min exposure when the contact temperature is below 43° as well as the sharp margins of the manifest wheals may indicate that a certain temperature level is required for formation of the wheal producer. An acetylcholine release occurring in tissues without a certain temperature elevation would then not induce an urticarial reaction. The negative result with warmed serum i.d. tests also strengthens such an assumption.

The mechanism for the delay of the whealing is also unknown. Possible explanations could be either a slow initial formation of the wheal-producing factor or, if the primary events start a chain of reactions involving histamine release, a plasma leakage and dilution with subsequent kinin formation. The biopsy findings showed an inflammatory reaction which is much more pronounced than in acute urticaria where histamine is thought to be the main mediator and this strengthens the assumption that several steps and mediators are involved in this urticarial reaction. A similar inflammatory reaction is seen in chronic

urticaria where the kallikrein-kinin system is believed to be an important mediator (7). The time course for whealing in our patient is similar to that seen after intradermally injected kallikrein which, in this age group, begins to develop after 1 to 2 hours and reaches its peak after 5 hours.

The role of the basophils as producers of the vasodilator histamine after heat stimulation has been discussed by Shelley (13). If such a mechanism is valid here, the high percentage of degranulated basophils found in our patient need not be the result of an allergic reaction, but might be due to an increased sensitivity to heat.

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Received December 30, 1970

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