

Familial cholinergic urticaria

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Cholinergic urticaria (CU) is a common variant of the physically induced types of urticaria. It accounts for about 30% of all cases of the physically induced types of urticaria and for nearly 7% of all the types of chronic urticaria.¹

The hallmarks of the disease are pruritic wheals, which are distinctive, monomorphic, and punctate; 2 to 3 mm in size; and surrounded by a bright rash.^{1,2} Usually, the rash appears on the upper trunk, face, and arms 5 to 15 minutes after a trigger event and lasts 20 to 30 minutes. Several external physical triggers, all of which raise the body core temperature, are known to induce this phenomenon.²

The cause of CU is unknown, but high serum histamine levels have been detected during attacks.³ To the best of our knowledge, familial cases have not been previously described. Herein we present four families characterized by CU since early adulthood and manifested in male family members only.

METHODS

Subjects

Members of four families with CU attended the Allergy Unit of the Tel-Aviv Sourasky Medical Center during the past 7 years. This is a nationwide referral center for allergy, particularly for army personnel.

One family has been under our care for the past 7 years, whereas members of the three other families were referred for consultation only and are currently followed up by other allergists. All patients underwent a comprehensive clinical evaluation, including a complete physical examination before and after a trigger event. Two provocation tests were used for diagnosis, as recommended by Commens and Greaves.⁴

Exercise test

The patients ran on a Quinton treadmill (Quinton, 18-54, Washington, U.S.A.) at a speed of 4 mph and a gradient of 15% for a total of 10 to 15 minutes, or until

Abbreviation used

CU: Cholinergic urticaria

symptoms appeared. The skin was examined during the exercise and 30 minutes after it.

Intradermal methacholine test

Methacholine (Sigma Chemical Co., St. Louis, Mo.) was introduced intradermally at a concentration of 0.1 mg/ml. The wheal response was measured 10 to 15 minutes later. The presence of pseudopods was considered as a positive response.

RESULTS

All patients had typical symptoms of CU, confirmed by results of both exercise challenge and intradermal methacholine test. Patient and disease characteristics are summarized in Table I.

Family 1

The six members (2 parents, 1 daughter, and 3 sons) of Family 1 were all born in Israel. The grandparents originated from the Afghanistan-Iran area. The father (patient 1) and one of the three sons (patient 2) have CU, and all other family members have no clinical symptoms that could be related to urticaria of any type. In both patients the symptoms started at 16 years of age. The condition of the father, now 65 years old, had improved over the years. The son, now 18 years old, is still experiencing symptoms.

Family 2

There were seven members in this family (2 parents and 5 siblings). The father was born in Afghanistan, the mother in Iran, and all children in Israel. Two of the children are boys, and both have CU (patients 3 and 4). They have had symptoms from the age of 16 years and have continued to experience symptoms until the present (for 7 and 4 years, respectively).

Family 3

This family consists of two parents and four siblings. Both parents were born in Yemen, and all children were born in Israel. The father (patient 5) and the two sons (patients 6 and 7) have had mild symptoms of CU since the age of 17 or 18 years.

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J Allergy Clin Immunol 1996;98:847-9.

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0091-6749/96 \$5.00 + 0 1/54/75631

TABLE I. Patient and disease characteristics

Family	Patient No.	Age at onset (yr)	Duration of illness (yr)	Triggers	Rash site	Main season	Duration of attack (min)*
Family 1							
Father†	1	16	40	Heat, spicy food	Back	Summer	30
Son	2	16	2	Heat	Neck, chest, face	Summer	20
Family 2							
Son	3	17	7	Heat, anxiety	Total body	Winter	20
Son	4	17	4	Heat	Neck, chest, arms	All year	20
Family 3							
Father‡	5	17	43	Heat	Total body	Winter	10
Son	6	17	2	Heat, anxiety, exercise	Abdomen, chest, arms	All year	15
Son	7	17	8	Heat	Chest, arms	All year	20
Family 4							
Son	8	21	4	Anxiety	Face, arms, chest	All year	30
Son	9	21	6	Heat, anxiety	Face, arms, chest	All year	20

*Duration of average episode of urticaria.

†Also has aquagenic urticaria and dermographism.

‡Also has rhinitis.

However, unlike the father who had overt symptoms for 2 years only, the sons have had clinically active symptoms for the past 2 and 8 years, respectively.

Family 4

The two parents immigrated from Romania to Israel, where their two sons were born. Both sons (patients 8 and 9) have had symptoms from the age of 21 years, with progressive severity of disease manifestations since (approximately 4 to 6 years).

All our patients with CU were troubled by their symptoms and required repeat courses of H1-blockers. Both members of Family 2 who have CU are taking hydroxyzine daily (25 to 100 mg) with occasional short courses of low-dose prednisone.

DISCUSSION

CU is a common variant of urticaria. Although it is common among young adults, with 10% to 20% of them exhibiting this rash in a mild form, no familial clusters have been reported.^{2,5} To the best of our knowledge, the four families described herein represent the first report of familial occurrence of CU. Onset of symptoms in patients with CU is usually between age 15 and 25 years.² A similar age of onset was observed in all of our patients: seven of them (patients 1 to 7) were first seen with symptoms at age 16 to 17 years, and the other two (patients 8 and 9), at age 21 years. Interestingly, all members of one particular family had an identical age of onset. CU seems to affect male and female patients to the same extent. Zuberbier et al.⁵ have recently pointed out a higher prevalence among women. This was not corroborated by any statistical evaluation. In our cases all affected patients were

male, and a father-to-son transmission rules out an X-linked inheritance. This is suggestive of autosomal dominant inheritance. Several external factors known to raise the body core temperature have been implicated in the pathogenesis of CU. The most common ones include immersion in a hot tub, excessive room temperature, exercising while wearing occlusive clothing, and emotional stress, all of which induce sweating.¹ In fact, all our patients clearly stated that symptoms were induced by either heat or anxiety. One patient (number 1) reported spicy food as an additional important trigger. All our patients have the mild-to-moderate form of this condition. Only one of our patients (number 5) has an atopic condition (rhinitis). Combinations of several types of urticaria were frequently reported in the literature,² but only one of our nine patients exhibited other forms of urticaria: patient number 1 reported aquagenic urticaria and dermographism, both reproduced in our laboratory. It should be noted that only two of our patients (numbers 1 and 2) described aggravation of symptoms during the summer, whereas there was no seasonal variation in the remaining ones.

The natural history of CU is variable, with most cases undergoing spontaneous resolution over a period of several years. Sibbald² estimated the average duration as 7.5 years (range, 3 to 16 years). The younger male patients in our survey, who are now 19 to 25 years old, have had symptoms for the past 2 to 8 years. Our older patients, the fathers (numbers 1 and 5), exhibited mild symptoms for several decades. The reason for this protracted course is not clear, but it does parallel the lengthy durations described for the other familial forms of urticaria lasting up to 40 years.²

In conclusion, we have presented four familial cases of CU. Our patients do not share a common genetic background: some are Sephardic Jews, and the others are of Ashkenazi extract. The affected individuals are exclusively male with father-to-son transmission and a similar age of onset. In this set of families, the cause may well be a major autosomal dominant gene in a polygenic background with an environmental trigger. Their signs and symptoms are similar to those of patients with classic CU as described in the literature. All our patients have had active disease since adulthood: the older ones, the fathers, for several decades and their sons, for several years since the onset of symptoms. The long duration of symptoms might be an exclusive feature of the familial types of urticaria.

We thank Ceryl Legum, MD, Head of the Department of Genetics, Tel-Aviv Sourasky Medical Center, for his suggestions and guidance in the preparation of this article.

REFERENCES

1. Tariq M. Physical urticarias. *Am Fam Physician* 1994;49:411-4.
2. Sibbald RG. Physical urticaria. *Dermatol Clin* 1984;3:57-69.
3. Sorer NA, Wasserman SI, Austen KF, McFadden ER. Release of mast-cell mediators and alterations in lung function in patients with cholinergic urticaria. *N Engl J Med* 1980;302:604-8.
4. Commens CA, Greaves MW. Tests to establish the diagnosis in cholinergic urticaria. *Br J Dermatol* 1978;98:47-51.
5. Zuberbier T, Althaus C, Chantraine-Hess S, Czarnetzki BM. Prevalence of cholinergic urticaria in young adults. *J Am Acad Dermatol* 1994;31:978-81.

Cefazolin specific side chain hypersensitivity

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At our adverse drug reaction clinic in the past 9 years, over 1000 patients have been skin tested for possible penicillin allergy with benzylpenicillin, penicilloyl-polylysine, minor determinant mix, ampicillin (1 mg/ml), and cefazolin (1 mg/ml). Our overall skin test positivity rate is 4%, which is in keeping with that reported in the world literature.¹ Our cefazolin skin test positivity rate is 0.9%. Of our nine patients with positive cefazolin skin test results, only one had positive responses exclusively to cefazolin, whereas the rest had positive responses to other penicillin determinants in addition to cefazolin.

CASE REPORT

The patient with the isolated cefazolin positive skin test result was a 33-year-old woman who experienced anaphylaxis (severe hypotension, bronchospasm, urticaria, abdominal pain, nausea, and vomiting) within 15 minutes of intravenous administration of 1 gm of cefazolin before surgery. She had no history of β -lactam allergy and had received ampicillin in the past without experienc-

ing an adverse reaction. She may have been exposed to cefazolin previously because she had undergone other orthopedic procedures, but this has not been confirmed.

Skin testing 4 months after the acute event revealed an isolated positive intradermal skin test response to cefazolin (1 mg/ml) with negative intradermal skin test responses to benzylpenicillin, penicilloyl-polylysine, and minor determinant mix, as well as to ampicillin, cefotetan, ceftriaxone, cephalothin, cefuroxime, and ceftazidime (all at a concentration of 1 mg/ml). The cefazolin intradermal skin test site showed a 35 mm erythematous flare reaction accompanied by a 5 mm increase in the size of the wheal from an initial 6 mm to a final 11 mm in diameter. All other intradermal sites showed no flare or change in the size of the wheal. Results of subsequent oral challenges with full-dose penicillin VK, amoxicillin, cefaclor, cefuroxime axetil, and cephalexin were also negative, confirming her tolerance to other β -lactams and supporting the hypothesis that this represented a side chain-specific cefazolin allergy.

DISCUSSION

Side chain-specific β -lactam allergy exists when IgE antibody is directed toward the unique side chain of a particular β -lactam antibiotic rather than the common β -lactam ring.² Our patient fits this model with evidence of allergy to cefazolin but tolerance to a wide variety of other β -lactams as determined by skin testing and oral challenges.

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J Allergy Clin Immunol 1996;98:849-50.

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