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Response to intradermal injection of monosodium urate crystals in Behçet's syndrome

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Abstract

The cutaneous response to intradermal injection of monosodium urate crystals was investigated in 97 patients with Behçet's syndrome in Turkey and 14 in the United Kingdom, and in 82 healthy and 88 diseased controls. Urate crystals produced an increased erythematous response in patients compared with controls in both countries. This response was different from that of the pathergy test performed at the same time. The systemic acute phase response, studied only in Turkey, showed no differences between patients and controls.

Intradermal injection of monosodium crystals causes local and systemic responses.[1–3] Patients with Behçet's syndrome have the potential for increased cutaneous inflammatory activity shown by sensitivity to a needle prick (the pathergy test). The pathergy phenomenon is seldom seen among English patients with Behçet's syndrome, however, though other clinical findings are similar.[5 6]

We tested the hypothesis that the cutaneous response to intradermal injection of urate crystals is greater in patients with Behçet's syndrome than in healthy and diseased controls and is both specific to, and sensitive in, the diagnosis of Behçet's syndrome. The systemic response to urate crystals was also assessed in Turkish patients.

Patients and methods

All patients studied fulfilled the diagnostic criteria for Behçet's syndrome recommended by Mason and Barnes[7] and O'Duffy.[8]

STUDIES IN TURKEY

Urate crystals were prepared by a modification of Seegmiller's method.[2] Pure uric acid (1·68 g) was added to 400 ml of boiling distilled water and adjusted to pH 8 with 0·5 N NaOH. This supersaturated solution was kept at room temperature for 24 hours to allow the crystals to precipitate. The crystals were then baked at 180°C for three hours. Immediately before use the desired amount of crystals to be injected was suspended in 0·2 ml sterile normal saline, briefly sonicated, and checked by polarised light microscopy. The initial experiments to determine the cutaneous and systemic responses to 10 mg urate in Turkey used crystals supplied by Professor P Dieppe (Bristol, UK).

Urate crystal suspensions were injected intradermally into the flexor surface of the non-dominant forearm. An equal volume of normal saline was injected into the opposite forearm. The pathergy test was also performed on the non-dominant forearm.[4] The erythema which developed at each site was measured by weighing a paper template (using standard paper throughout) of the area at 24 and 48 hours after injection.[9] The erythema was thus recorded as the weight of the paper in milligrams. Some patients and controls had erythrocyte sedimentation rate, total and differential leucocyte count, C reactive protein, and prealbumin concentrations estimated before and 24 and 48 hours after the urate injections. Body temperature was also recorded.

STUDIES IN ENGLAND

The urate crystals were prepared by a similar method in Professor Dieppe's laboratory (Bristol, UK), and the same clinical methods were used. No haematological or biochemical tests were performed.

Results

Ninety seven Turkish and 14 English patients with Behçet's syndrome, and 170 normal or diseased controls who gave informed consent to the investigation were studied. Table 1 shows the different quantities of urate crystals given by intradermal injection.

STUDIES IN TURKEY

Initially, 10 mg of urate crystals was injected intradermally into the forearm of 25 patients with Behçet's syndrome and 31 healthy controls. It was noted that at 48 hours the mean area of erythema in the patients was significantly greater than in controls ($t=2·75$, $p<0·01$), whereas they had been similar at 24 hours (figure). It was also found that the C reactive protein and erythrocyte sedimentation rate values before and after injection were significantly raised and the prealbumin concentrations depressed in patients compared with controls. Urate crystal injection was not associated with alterations in C reactive protein concentrations, erythrocyte sedimentation rate, white blood cell counts, or body temperature. Prealbumin concentrations both in female patients and female controls were affected at 24 hours, however. The mean (SD) baseline prealbumin concentrations of 185·0 (50·1) mg/l for patients and 226 (63) mg/l for controls decreased to 155 (50) mg/l ($p<0·01$) and 205 (38) mg/l ($p<0·05$) respectively. These returned towards baseline values

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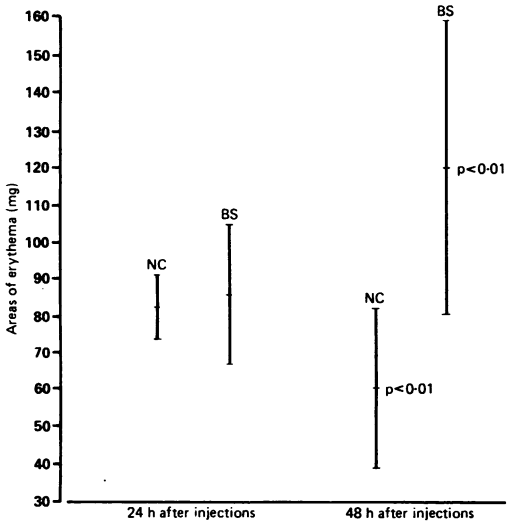
Table 1 Patients and controls studied

Country	Urate received (mg)	Behçet's syndrome			Normal control			Diseased control		
		n	*F*	*M*	*n*	*F*	*M*	*n*	*F*	*M*
Turkey	10	25	15	10	31	18	13			
	3	8	5	3	10	6	4			
	2	23	12	11	22	3	19			
	1	5	—	5	8	6	2			
	2·5	36	19	17				72	36	36
Total		97	51	46	71	33	38	72	36	36
England	2·5	14	9	5	11	8	3	16	12	4



95% Confidence limits for the areas of erythema (measured in mg) in 25 patients with Behçet's syndrome (BS) and in 31 normal controls (NC) 24 and 48 hours after injection of urate crystals (10 mg).

at 48 hours. No change in the prealbumin concentrations was noted at 24 hours in male patients or male controls. The baseline prealbumin concentrations of female controls were significantly lower than those of male controls (226 (63) mg/l *v* 297 (98) mg/l; $p<0·025$). This difference was not found among patients.

Thereafter decreasing amounts of urate crystals were used in further patients and controls. At the lower doses used not all patients and controls showed the erythematous response seen in all subjects with the 10 mg dose. A dose-response pattern was seen (table 2). It was extrapolated from these data that optimum sensitivity and specificity in patients with Behçet's syndrome might be achieved with 2·5 mg urate crystals. This dose was studied in a further 36 patients with Behçet's syndrome and in 72 patients with various other diseases (table 3) with almost 100% specificity and 61% sensitivity for Behçet's syndrome. In this group all patients and controls also had pathergy tests

Table 2 Areas of erythema at 48 hours with different amounts of urate crystals

	Behçet's syndrome			Normal controls	
	Number	Positive response No (%)	Erythema (mg) Mean (SD)	Number	Positive response
3 mg	8	8 (100)	50·4 (31·5)	10	Only two: 7 mg and 8 mg
2 mg	23	16 (70)	38·5 (37·7)	22	None
1 mg	5	3 (60)	11, 30, 40	8	None

Table 3 Response to urate crystals (2·5 mg) at 48 hours in Turkish patients with Behçet's syndrome and diseased controls. Results are given as means (SD)

Disease	Age	Positive pathergy	Positive urate reactions at 48 hours	
			No	mg
Behçet's syndrome (n=36)	35·6 (8·7)	17†	22§	46·2 (30·4)¶
Diseased controls* (n=72)	39·5 (13·5)	4‡	None	—

*Rheumatoid arthritis (20), ankylosing spondylitis (nine), familial Mediterranean fever (seven), systemic lupus erythematosus (six), gout (six), vasculitis (four), erythema nodosum (three), sarcoidosis (three), emphysema (three), pulmonary tuberculosis (two), juvenile rheumatoid arthritis (two), palindromic rheumatism (two), acute rheumatic fever (one), myositis (one), osteomyelitis (one), anterior uveitis (one), cirrhosis (one).
†Three had no response to urate crystals.
‡Acute rheumatic fever, sarcoidosis, emphysema.
§Eight had no response to pathergy.
¶These are the mean values of the positive results only.

Table 4 Results of pathergy and urate crystal studies in English patients with Behçet's syndrome, with other rheumatic diseases, and in normal controls. Results are given as means (SD)

Subjects	Age	Positive normal saline	Positive pathergy	Positive urate crystals	Areas of erythema (mg)
Behçet's syndrome (n=14)	38·2 (14·9)	2 (2 mm and 10·5 mg)	4	13‡	69·98 (59·98)
Rheumatoid arthritis (n=12)	63 (9·8)	1 (8·6 mg)	2*	3§	72·14 (66·42)
Ankylosing spondylitis (n=4)	37·25 (9·6)	None	None	1	94·46
Normal controls (n=11)	35·1 (8·9)	1 (2–3 mm)	1†	2	7·38

*One had no response to urate.
†Urate response was negative.
‡Four had positive pathergy.
§One patient had positive pathergy.

performed, of which 17/36 (47%) and 4/72 (5%) respectively were positive.

STUDIES IN ENGLAND

Fourteen patients and 27 controls of English descent were given 2·5 mg urate and studied similarly (table 4). An erythematous response to urate crystals developed in 13/14 (93%) patients and 6/27 (22%) diseased and healthy controls ($\chi^2=15{\cdot}02$, $p<0{\cdot}0001$). The pathergy test was positive in 4/14 (28%) patients and 3/27 (11%) controls, which was not significant.

Discussion

This study compared the cutaneous response to an intradermal injection of urate crystals in patients with Behçet's syndrome with that in healthy and diseased controls. The results show that at high dose (10 mg) all control subjects and patients with Behçet's syndrome produce an erythematous response, which is greater at 48 hours in patients with Behçet's syndrome than in controls. As the dose was reduced a level was reached at which erythema did not occur in healthy controls but did occur in Behçet's syndrome, which seemed to be highly specific. Notably all seven patients with familial Mediterranean fever had negative responses to urate crystals, though increased leucocyte activity is also well recognised in this condition.[10]

The same test in England gave similar but not identical results. In English patients an erythematous response to urate developed in 4/16 (25%) patients with common rheumatic diseases and in 2/11 (18%) healthy controls. This makes the urate crystal test less useful diagnostically in English patients. The different response of English subjects to urate crystals may be due to (*a*) the small number of patients studied from whom this conclusion was drawn; (*b*) the different source of urate crystals used; and (*c*) possible ethnic differences.

There was no evidence that systemic responses to intradermal urate crystal injections were greater in patients than in controls. Serum prealbumin concentrations have not previously been reported in Behçet's syndrome. This study showed a slight decrease in prealbumin among patients. The difference in baseline prealbumin concentrations in healthy male and female subjects had previously been noted.[11]

Augmented response to urate crystal injections at 24 hours only among the female patients and female controls is, we believe, a new observation, however. The skin response to urate crystals and the pathergy reaction are probably not the same phenomenon as (1) The morphology of the skin response is different. The pathergy reaction is a papule or pustule, whereas the urate reaction is an erythematous area, which almost never pustulates (only one English patient had a pustular reaction). (2) There were 11 Turkish and 9 English patients in whom the results of the tests were different (tables 3 and 4). (3) A positive pathergy reaction is uncommon in English patients, though clinical manifestations are similar to those of their Turkish counterparts.[5 6] Their response to urate crystals, however, was similar to that of Turkish patients.

Behçet's syndrome is the only rheumatic condition in which, to date,[1] an augmented response to intradermal injection of urate crystals is seen. This response may be useful diagnostically.

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