

Diagnosis of Behçet's Disease in a Non-endemic Region

The Utility of the Urate Skin Test

C Flower

ABSTRACT

Sporadic cases of Behçet's disease in non-endemic regions pose a diagnostic challenge and may be confused with other more common chronic, relapsing multisystem disorders. The urate skin test, an exaggerated inflammatory reaction to intradermally injected monosodium urate crystals, may add a level of diagnostic specificity to a disease which otherwise lacks pathognomonic clinical features.

Diagnóstico de la Enfermedad de Behçet en una Región no Endémica

la Utilidad de la Prueba Cutánea de Ácido Úrico

C Flower

RESUMEN

Los casos esporádicos de la enfermedad de Behçet en regiones no endémicas, plantean un desafío diagnóstico y pueden ser confundidos con recidivas de otros trastornos multi-sistémicos crónicos más comunes. La prueba cutánea de ácido úrico – una reacción inflamatoria exagerada de cristales de urato monosódico inyectados intradérmicamente – puede elevar el nivel de especificidad diagnóstica en relación con una enfermedad que, por lo demás, carece de características clínicas patognomónicas.

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Behçet's Disease Overview

From its original description by Turkish dermatologist Hulusi Behçet in 1937, the cardinal features of Behçet's disease initially described were orogenital ulceration and ocular inflammation (1). The disease spectrum has now expanded to include inflammatory processes in the skin, joints, nervous system, gut and blood vessels (2). The disease, with a mean age of onset of 20–35 years, is more severe in men and has a recognized association with HLA-B51. There is sporadic familial clustering. The endemic areas described as the 'ancient Silk Road' include countries in the Mediterranean Basin and Asia, most notably, Turkey and Japan (3).

The International Study Group Criteria for the diagnosis of Behçet's disease (Table 1), developed in 1990, requires the presence of recurrent oral ulceration along with the presence of two of four criteria: genital ulcers, eye lesions, skin lesions and pathergy (4). The Behçet's Disease Research Committee of Japan developed revised criteria in 2003 because of suspected over-diagnosis of the disease

Table 1: The international study group for Behçet's disease diagnostic criteria 1990 requires patients to have recurrent oral ulcers and at least two other features.

Clinical criterion	Typical frequency in BD* (%)
1 Recurrent oral ulcers	At least 3 episodes per year. Minor aphthous, major aphthous or herpetiform ulceration. 100
2 Recurrent genital ulcers	70–80
3 Eye disease	Uveitis, retinal vasculitis, cells in the vitreous 45–75
4 Skin disease	Erythema nodosum, folliculitis, acneiform lesions outside adolescence, papulo-pustular lesions 70–95
5 Positive pathergy test	Vesicular lesion larger than 2 mm, 24–48h after skin prick with 20–22 gauge needle penetrated to 5 mm 5–75

*BD = Behçet's disease

From: Queen Elizabeth Hospital, Martindale's Road, St Michael, bb 11155 Barbados.

Correspondence: Dr C Flower, Queen Elizabeth Hospital, Martindale's Road, St Michael, bb 11155 Barbados. Fax: (246) 436-6450, E-mail: cflowerami@sunbeach.net.

based on those of the International Study group. These criteria report Behçet's disease as 'complete' if the four major features (oral ulcer, genital ulcers, ocular inflammation and skin disease) are all present. The presence of three major

features or two major features along with two other compatible features (*eg* arthritis, gastrointestinal disease, vasculitis and epididymitis) is described as 'incomplete Behçet's'. Patients with only a single major feature along with one or more additional features constitute the 'suspected' cases (5).

The diagnosis of Behçet's disease can be challenging. As with other rare diseases, sporadic cases in non-endemic regions may go unrecognized. Additionally, the diagnosis may rely heavily on the physician's clinical judgment because of the absence of pathognomonic features and diagnostic blood tests. Often more common illnesses such as inflammatory bowel disease must also be excluded (6).

Pathergy, a hypersensitivity of the skin to a sterile prick, typically assessed on the forearm, is considered a unique feature. However, it is found to be demonstrable in only 50% of cases and shows geographical variation with lowest incidence in Western countries (7).

The tendency in Behçet's disease for an abnormal inflammatory cutaneous response is also evident in the occurrence of false positive Mantoux tests (8). This can be particularly challenging in the assessment of cases with clinical features such as ocular inflammation and erythema nodosum which may occur in both Behçet's disease and tuberculosis. A more specific test for Behçet's disease would therefore be useful. The urate skin test started as a hypothesis combining the known cutaneous hyper reactivity in Behçet's disease with the previously demonstrated inflammatory response in individuals to intradermally injected crystals (9).

The urate skin test (Fig. 1), an augmented inflammatory response to intradermally injected monosodium urate crystals



Fig. 1: Monosodium urate skin test.

The ampoule contains 10 mg /1 ml monosodium urate (MSU) crystals and is shaken before use. With a 23 gauge needle, 0.2ml of MSU crystals is injected intradermally into the forearm. At 48 hours, erythema greater than 10 mm diameter is a positive response.

(0.2 ml of a 10 mg/ml solution) was described in 1991, in British and Turkish patients (10). The urate crystals are typically derived by the Modified Seegmiller's Method (11) where uric acid is allowed to precipitate out of solution followed by a process of baking of the urate crystals and

finally suspension in a saline solution. An erythematous intradermal reaction widely occurred when 10 mg of urate was used in a population of patients with Behçet's, other rheumatic diseases and healthy controls. However, the patients with Behçet's had a more marked reaction, prolonged past 24 hours. When the dose of the urate crystals was lowered to approximately 2 mg injected intradermally on the flexor aspect of the non-dominant forearm, patients with Behçet's tended to have a continued reaction, maximal at 48 hours while patients who were healthy or had other rheumatic conditions did not. This was particularly striking in the Turkish arm of the study where the sensitivity and specificity of the urate skin test was found to be 68% and 99% respectively (12).

When a smaller number of British patients was studied, 93% of patients with Behçet's disease had a positive urate test compared to 22% of healthy and disease controls suggesting a decreased specificity of the test in this population (10). The disease controls had such conditions as rheumatoid arthritis and ankylosing spondylitis.

It is thought that the urate skin test and pathergy reaction are not the same phenomenon. There is an erythematous response in the former and a papulopustular response to the latter. The results of these tests in any given individual may also be discordant.

Local experience

Between 1997 and 2006, three patients seen by the rheumatology service of the Queen Elizabeth Hospital, Barbados, and thought to have Behçet's disease, were documented to have positive urate skin tests. The clinical features are tabulated (Table 2).

Table 2: Clinical features of Behçet's disease in 3 patients.

	Case 1	Case 2	Case 3
Age at diagnosis (years)	48	34	33
Duration of symptoms (years)	2	15	17
Sex	Male	Female	Male
Race	AC*	AC	AC
Oral ulcers	+	+	+
Genital ulcers	-	+	-
Ocular lesions	-	+	+
Skin lesions	+	+	+
Arthritis	+	-	-
Pathergy	-	-	-
Positive urate skin test	+	+	+

*AC = Afro Caribbean. + = present - = absent

Case 1

A male Barbadian presented at age 48 years with a two-year history of frequent recurrent oral ulceration, an eighteen-month history of intermittent joint pain with swelling and a four-month history of recurrent skin lesions on the arms. There was no history of genital ulcers or ocular inflammation. On examination, there were ulcers on the buccal

aspects of the lips and papulopustular lesions on the upper limbs.

He was seronegative for HIV antibody, VDRL was non-reactive and screen for *Chlamydia trachomatis* antibody was not significant. Rheumatoid factor and antinuclear antibody were negative. Chest X-ray was normal, barium studies were negative for inflammatory bowel disease. On subsequent review, the patient was also documented to have small joint effusions at the knees, swelling around the ankles, erythema nodosum-type lesions on the legs, palatal ulcers and pustular lesions also on the skin of the thighs and the abdomen.

Treatment with prednisolone and azathioprine for a presumptive diagnosis of Behçet's disease resulted in remission of his symptoms. Flares of the above symptoms occurred but only related to non-compliance with medication. When available to be performed, the urate skin test was positive with an erythematous reaction greater than 1cm at 48 hours (Fig. 2).

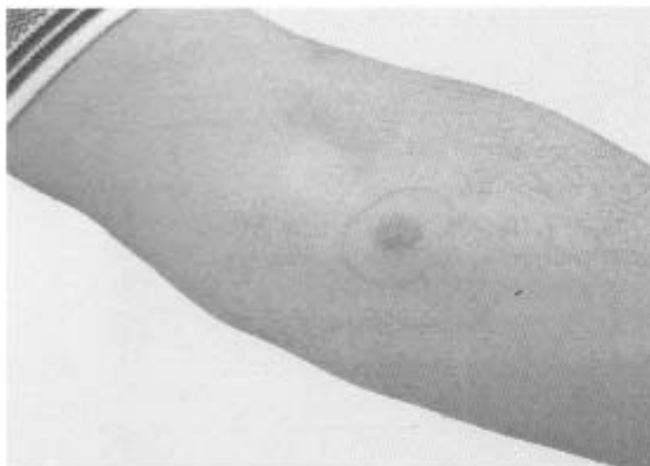


Fig. 2: Positive urate skin test (case 1). An erythematous reaction to intradermally injected monosodium urate crystals.

Case 2

A female Barbadian presented at age 34 years with a 15-year history of recurrent severe oro-genital ulceration, pustular skin lesions and ocular inflammation initially diagnosed as Stevens Johnson syndrome. There were negative tests for HIV and herpes simplex virus.

The patient also noticed an exaggerated response to insect bites with the development of fine papules around the affected area. She was referred to the rheumatology clinic in 2001 after being diagnosed with scleritis of the left eye.

On review of her medical history, a diagnosis of Behçet's disease was made and her disease has since been controlled on azathioprine. The urate skin test performed in March 2006 was positive.

Case 3

A male Barbadian presented at age 33-years with acute bilateral posterior uveitis and a history of recurrent oral ulceration for several years. Initial investigations revealed negative HIV antibody, toxoplasmosis titres, ANA and ACE level and non-reactive VDRL. The Mantoux skin test was negative. Chest X-ray was normal. Barium studies did not reveal evidence of inflammatory bowel disease. The ESR was elevated at 57 mm/hr (Westergren). Over the period of follow-up, he was observed to have pustular skin lesions especially at sites of minor trauma. No genital ulcers had been documented. The patient is currently maintained on oral methotrexate for his ocular disease. The urate skin test was positive.

DISCUSSION

Barbados, a 166 square mile island in the eastern Caribbean, has a population of 270 000 of whom 92% are of African descent, 6% are Caucasian and 2% are Asian (2000 census). With the acknowledgement that there is a low incidence of HLA B51 in west African and Afro-Caribbean populations, a decreased risk of Behçet's disease in these ethnic groups is expected (13). However, the true disease prevalence in native Afro-Caribbean people is unknown and case reports are limited. A review of 13 cases of Behçet's disease from Guadeloupe (French West Indies) suggests that the frequency may be higher than previously thought (14). The highest incidence as reported in endemic areas is 1–10 cases per 10 000 population compared with 1–2 cases per 1 000 000 population in the USA and the UK (5).

The course of Behçet's disease is that of a relapsing and remitting chronic illness. The typical initial symptom is oral ulceration followed chronologically by genital ulceration and articular symptoms. There is usually a time period of several years between the initial clinical feature and fulfillment of criteria for diagnosis but this period is often shorter in the individuals with serious organ involvement and eye disease (15). Eventually, the disease burden appears to diminish with the passage of time.

The most characteristic ocular lesions in Behçet's disease are iridocyclitis, hypopyon, vitreitis, retinal vasculitis, optic disc hyperaemia and macular oedema with the anterior lesions having a good prognosis and the posterior lesions being associated with varying degrees of visual loss (16). Eye involvement is typically bilateral, though the severity in each eye may differ. Less commonly, as in one of index cases, scleral disease has been described (17). Conjunctival ulcers were noted to affect 26% of patients in a report from India (18) but conjunctivitis is known to be rare. Papulopustular skin lesions were the most common cutaneous lesions in our patients, as is typical in Behçet's disease. The presence of lymphocytic vasculitis on biopsy of such lesions may be useful in distinguishing between

Behçet's disease and other causes of papulopustular lesions such as folliculitis and acne vulgaris (19). One patient was documented to have articular involvement, a complication described in 68% of patients in one study (20). Knee and ankle involvement is known to be most common and has an association with erythema nodosum. In non-endemic areas where Behçet's disease is infrequently seen and where there is a likelihood of presentations with milder disease, the urate skin test can be a useful adjunct to the composite of clinical features important for diagnosis. Though the test sensitivity does not allow its use as a screening tool, the very high specificity is useful in excluding diseases with similar clinical features.

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