Chapter 2
History and Diagnosis

Colin G. Barnes

Keywords Aphthous ulceration • Behçet’s disease • Behçet’s syndrome • Classification • Diagnostic criteria • Pathergy • Vasculitis • Vasculopathy

Introduction

The eponymous name of Behçet’s Syndrome (BS) was derived from the description of the “Triple Symptom Complex” by Professor Hulusi Behçet [1–3]. He described the association of oral and genital ulceration with uveitis and considered this to be of possible viral aetiology.

Biographies of Hulusi Behçet (1889–1948), written by Professor Türkan Saylan, have been published in the proceedings of an International Conference on Behçet’s Disease held in Istanbul in 1977 [4], and in the Yonsei Medical Journal (1997) [5] the latter demonstrating the great interest in the condition in Korea. Professor Nihat Dilşen also wrote a short biography, and reviewed the development of knowledge of the syndrome between the fifth century BC and 1996, in the proceedings of the 7th International Conference on Behçet’s Disease, Tunis [6].

Behçet was born in Istanbul but educated in Damascus where his family lived, and then studied medicine at the Turkish Gülhane Military Medical Academy qualifying at the age of 21 years. Subsequently he specialised in dermatology and venereology and during the first World War served at the Edirne Military Hospital. He gained post-graduate experience in Budapest and Berlin and returned to Istanbul to practise dermatology and venereology. After the formation of the University of Istanbul in 1933 he became its first Professor of Dermatology and was responsible for the development of the Department of Dermatology. He was a prolific writer and enthusiastic teacher; he retired in 1947 and died a year later.

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He described three patients the first of whom he is said to have met in 1924–1925. These patients had the three principal features of aphthous ulceration and genital ulceration with inflammatory eye disease. However, although he described this as a “triple symptom complex,” and one can comment that he described many signs in his patients and not only their symptoms, he did also record erythema nodosum in one patient and acneiform lesions on the back of another. Behçet himself, therefore, described the four major features of the condition (orogenital ulceration, inflammatory eye disease and skin lesions). It is somewhat surprising that, as a dermatologist, he did not include skin lesions as the fourth feature of the syndrome he was describing. It is also surprising that he did not comprehensively refer to previous descriptions of similar patients, including some in the German dermatological literature having worked in Berlin and known to speak good German, in his own publications. He does refer to Lipschutz who had described what was considered to be viral diseases of the skin and one of Behçet’s patients had consulted Fuchs in Vienna, both of whom may have described the same syndrome in 1927 and 1926, respectively [7, 8].

The development of knowledge of BS, especially in the last 30 years, demonstrates that it has a different meaning to different interested groups. To the patient it is a problem which may last throughout life although there are records of self-limiting disease; to the physician it may be included in the differential diagnosis of occasional patients although large numbers of patients may be seen in some parts of the world; to the laboratory scientist it may be regarded as a model of disease expression involving inflammation and disturbances of immunity of uncertain aetiology.

**Early Descriptions of the Syndrome**

Like many diseases with eponymous names, Behçet was not the first to describe this association of clinical features. The first account probably dates back to Hippocrates in the 5th century BC. In *Epidimion*, Book 3, Case 7 (translated by Adams 1849 [9]) aphthous ulceration, genital ulceration and iridocyclitis are described. Additionally, reference was made to skin lesions – boils, sepsis, and “ecthymata”. Feigenbaum (1956) [10] commented that from this description it could be suggested that the condition was endemic, and possibly of epidemic proportions, in ancient Greece.

Our Chinese colleagues also record a description of a disease known as *Huo Ho Bing* by a Dr. Zhong Jing Zhang, c. 200 AD, which included pharyngeal ulcers, genital ulcers, eye redness and pus formation (skin) (Ohno, personal communication). From Europe and Japan in the late 19th century and early 20th century came descriptions of what would probably now be regarded as Behçet’s Syndrome (Table 1.1) [7, 8, 11–19]. Very small numbers of patients were described, for example a single case report from Adamantiades (who, in a subsequent paper, referred to Behçet’s Syndrome), with uveitis with or without hypopyon, and combinations of oral and genital ulceration and skin lesions. In some of these early
reports other clinical features, later accepted as integral manifestations of Behçet’s Syndrome, were also described including phlebitis, hydroarthrosis of the knees, and deep vein thrombosis [13].

Development of the Full Clinical Description of the Syndrome

Since the original description by Behçet the syndrome has developed such that the initial three manifestations have been further described in detail, skin manifestations have been included as the fourth major feature, and other features have been added as “minor” manifestations. These have been regarded as “minor” solely on the basis of occurring in <50% of patients and not as an indication of their clinical severity (Table 2.2). Vasculitis has been listed as a “minor” feature in the sense that it presents as a clinical feature, such as thrombophlebitis or aneurysm formation, although the condition is now regarded as being a systemic vasculitis, or vasculopathy, which is considered below. The approximate percentage prevalence of the manifestations listed in Table 2.2 is derived from various surveys including that of the International Study Group for Behçet’s Disease [20–23] but it must be emphasised that this varies in different parts of the world.

Aphthous Ulceration

Oral ulceration has been found to occur in 98% of patients with BS. The lesions are painful and may be major, minor or herpetiform types of ulceration as also occurs in benign Recurrent Oral Ulceration (ROU) [24, 25]. Ulceration may be preceded by the formation of a tender submucosal nodule. Major ulceration leads to mucosal scarring. Although the more serious forms of orogenital ulceration may raise the suspicion of BS it has been accepted that there is no diagnostically “typical Behçet’s ulcer”.

| Table 2.1 | Descriptions of possible Behçet’s Syndrome before 1937 |
|---|---|---|---|---|
| Speciality | Authors | Country | Year | Reference |
| | Shigeta | Japan | 1924 | [12] |
| | Fuchs | Austria | 1926 | [8] |
| | Adamantiades | Greece | 1931 | [13, 14] |
| | Dascolopoulos | Greece | 1932 | [15] |
| Internal Medicine | Chauffard et al. | France | 1923 | [16] |
| Dermatology | Neumann | Germany | 1894 | [17] |
| | Planner and Remenovsky | Germany | 1923 | [18] |
| | Lipschutz | Austria | 1924 | [7] |
| | Whitwell | United Kingdom | 1934 | [19] |
Mouth ulceration is the earliest manifestation of BS in the majority of patients and may be the presenting feature to the physician. In that oral ulceration may occur in up to 20% of western populations [26], and is the most common feature of BS, it is necessary that other features are present in order to contemplate a diagnosis of BS (see below), Similarly BS may commence with other features; 2–3% patients never develop oral ulceration. In other respects, the features of the syndrome are not significantly different between those with or without ulceration [27]. In paediatric BS in Korea it was found that all patients had oral ulceration and the authors recommended that aphthous ulceration in childhood required careful long-term follow-up [28].

It has been demonstrated in case studies that oral ulceration in BS is recurrent. In classification of the syndrome it has been arbitrarily accepted that recurrence is defined as occurring at least three times in one 12-month period [21–23].

Genital ulceration is regarded as following the same pattern as oral ulceration with respect to pain, initial tender nodule formation, major, minor and herpetiform types, recurrence and scarring [29]. Scarring of scrotal lesions is considered specific for BS.

**Eye Manifestations [30–33]**

The original description was of iritis/iridocyclitis with hypopyon to which has been added retinal vasculitis. The latter may lead to macular oedema, retinal haemorrhages and exudates, occlusion of retinal vessels both arteries and veins, vitreous haemorrhage and optic atrophy. Loss of visual acuity and complete blindness is, therefore, not uncommon although prognosis has been much improved by developments in treatment [34–36].
**Skin Lesions**

The skin lesions described in the early case reports, including by Behçet himself, were erythema nodosum and acneiform lesions [37]. These, with pustule formation and skin ulceration and scarring, have continued to be the principal reported lesions [38–40]. It is emphasised that to be significant in diagnostic terms acneiform lesions are more relevant when present in patients beyond puberty, in patients who are not taking systemic corticosteroid medication and, importantly, when present on the arms and legs – uncommon sites for common acne. It has also been shown that these acneiform lesions are not sterile and are often present in combination with arthritis [41]. However, as it became evident that BS should be classified as a vasculitis, or vasculopathy, the skin manifestations of superficial thrombophlebitis, papulopustular lesions, skin ulceration (non-genital), erythema nodosum and erythema multiforme-like lesions have been emphasised. Histological examination of mucocutaneous lesions may reveal a leucocytoclastic vasculitis with neutrophilia, extravasation of erythrocytes and fibrinoid necrosis [42–44].

**Pathergy Test**

The pathergy test, a hypersensitivity reaction to a sterile needle prick producing an erythematous papule, pustule or ulcer after 48 hours, was probably first described by Blobner [45] and Jensen [46]. Some investigators have claimed that the intradermal injection of 0.1 ml physiological saline produces a more reproducible response. However, this has fallen from popularity and simple, sterile, subdermal needle pricks are now used. This reaction was thought to be specific to BS and was found to be positive in the majority of patients. However the pathergy test:

- differs in the frequency of positivity in different countries being most common in Japan and Turkey and rare in western Europe [47–49],
- is more strongly positive in male patients [50],
- is more frequently positive in an individual patient if multiple needle pricks are applied some sites being positive and others negative [51],
- is more frequently positive if blunt, rather than sharp, needles are used [52],
- may be aborted if an antibiotic cream is applied after, or the skin is surgically scrubbed before, the needle prick [51, 53],
- is recorded as declining in frequency over the years,
- has been found occasionally in non-BS cases, for example in approximately 10% of patients with Crohn’s disease and 7% of patients with ulcerative colitis [54, 55] and
- may be present in first degree relatives of patients with BS [56, 57].

The cutaneous response to the intradermal injection of monosodium urate crystals appears to be different from the pathergy reaction [58].
Nevertheless a positive pathergy reaction has been included in several diagnostic criteria schemes and in the Classification of Behçet’s Disease by the International Study Group (see below).

**Joints**

Arthralgia and inflammatory synovitis have become accepted features of BS the latter occurring in approximately 45% of patients. Although arthralgia was reported in early descriptions the first report of joint swelling was probably in the 1930s. A synovitis was subsequently confirmed both clinically and histologically. It has been agreed universally that the knees are the most commonly affected joints followed by the ankles, wrists, elbows, small joints of the hands and wrists, shoulders, feet and hips. The arthritis has been variably described as monarticular, pauciarticular, polyarticular affecting an average of 5+ joints per patient, episodic and self-limiting [59–67].

Synovial pathology has been shown to be an acute neutrophilic inflammation with little, if any, synovial surface cell hyperplasia, plasma cell infiltration or lymphoid foci. It, therefore, resembles acute granulation tissue [68, 69] and differs from the more common inflammatory arthropathies characterised by rheumatoid synovitis. Rheumatoid factor test has always been found to be negative.

Initially it was thought that the synovitis was not destructive but later in a minority of cases erosive joint damage was reported clinically, radiologically and histologically [61, 69–73].

Additionally, occasional cases of avascular necrosis of the femoral head have been reported in patients not being treated with corticosteroids, presumably on the basis of a vasculitis (see below).

The presence of an associated sacroiliitis, and fully established ankylosing spondylitis, has been a question of considerable debate over the years. Sacroiliitis was described in up to 65% of patients in some series and it was suggested that the arthritis of BS should be grouped with the seronegative spondarthritides [74, 75]. However, although this suggestion raised the awareness of BS in rheumatological circles, it has not been supported by subsequent studies in which it has been demonstrated that sacroiliitis does not occur more frequently in BS than in normal subjects in the same population [76, 77]. The arthritis of BS, therefore, does not fall into the classification of seronegative spondarthritides (Table 2.3) as is discussed more fully in Chap. 9.

**Vasculitis/Vasculopathy**

Clinically the effects of vasculopathy have been detected as superficial (subcutaneous) thrombophlebitis, deep vein thrombosis, arterial occlusion or aneurysm formation and vena caval occlusion [78]. In 1977, of 1731 Japanese patients 133 (7.7%) had clinical evidence of vascular lesions. These affected both arteries and veins of all
sized with a 20% mortality. Histological examination of large vessels revealed thickening of the media, fragmentation of the elastica and perivascular round cell infiltration around the vasa vasorum [79–81].

By 1993, similar clinical findings were reported from China, Saudi Arabia, Turkey and Tunisia, and vasculitis was proposed as the underlying pathology of the syndrome [82–86].

Behçet’s Syndrome is now usually classified as a vasculitis which usually means injury or destruction of blood vessels. It is probably more accurate to call this a vasculopathy, an abnormality of blood vessels not necessarily leading to injury, which may affect arteries and veins of all sizes and in which there is an immunologically mediated impairment of vascular endothelial function [87–91].

### Pulmonary and Neurological Lesions

Vasculopathy is regarded as the cause of pulmonary and neurological lesions. In the early descriptions of patient with BS pulmonary lesions were rarely or never found. This has been summarised by Dilşen et al. [92] who noted that the first mention was by Dasculopoulos in 1932 [15], whereas Oshima et al., in their study of 85 Japanese patients, did not comment on pulmonary manifestations [60]. Shimizu, in his review of the syndrome at the International Symposium on Behçet’s Disease in 1977, derived from Japanese studies, described two single cases with pulmonary features of tuberculosis-like shadows. One, from the United States, did not respond to anti-tuberculous treatment and the other from Japan being attributed to vascular involvement. He also included a single case of aneurysm of the pulmonary artery among the vascular lesions which may have been the same Japanese patient [79].

These early descriptions listed pleural effusion, hilar enlargement, cavitating lesions, apical fibrosis or calcified lesions, and emphysema among the findings raising a query of whether these were coincidental or real features of BS [93–95].

Vascular lesions affecting the lungs are now well described and are the cause of pleuropulmonary manifestations of BS. Pulmonary artery occlusion or aneurysm formation with, often severe, haemoptysis are rare but potentially fatal manifestations

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<tr>
<th>Table 2.3</th>
<th>Comparison of the arthritis of Behçet’s Syndrome with seronegative spondarthritides</th>
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<tbody>
<tr>
<td>Behçet’s Syndrome</td>
<td>Seronegative spondarthritides</td>
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<tr>
<td>Vasculitis</td>
<td>+++</td>
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<tr>
<td>Pauciarticular – large joints</td>
<td>++</td>
</tr>
<tr>
<td>Asymmetry</td>
<td>±</td>
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<td>Spine/heel involvement</td>
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<td>Sacroiliitis</td>
<td>–</td>
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<tr>
<td>Family aggregation</td>
<td>±</td>
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<tr>
<td>Skin lesions</td>
<td>Erythema nodosum, acneiform lesions, thrombophlebitis</td>
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<td>HLA</td>
<td>B5(51)</td>
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seen mainly in young male patients. Pulmonary embolisation from thrombosis of deep leg veins is not thought to occur as the thrombus is attached to the vessel wall by the inflammatory process – thus being an inflammatory thrombophlebitis rather than a phlebothrombosis caused by stagnation. Anticoagulation is, therefore, to be avoided lest this leads to fatal haemorrhage from a pulmonary artery aneurysm [96–98].

Descriptions of neurological manifestations date back to 1944 [99] and have included spinal cord lesions, focal brain lesions, headaches and thrombosis and occlusion of dural sinuses, all on the basis of the underlying vasculitis [100–103]. Headaches were one of the earliest reported neurological features of BS [79] which has been confirmed by more recent studies. These headaches have been detected in up to approximately 80% of patients, fulfil internationally agreed criteria for the diagnosis of migraine but are not thought to necessarily indicate neurological pathology [104, 105]. Clinically the neurological features are those of a meningo-encephalitis affecting all parts of the central nervous systems including the brain stem and spinal cord [105]. Surprisingly, in view of the pathological confirmation of a vasculitis, involvement of the peripheral nervous system (mononeuritis multiplex) is not a feature of BS.

These clinical features have been confirmed by histopathology [105], and more recently investigation by MRI has enabled lesions to be demonstrated clinically [106–109].

**Gastrointestinal System**

Ulcerative lesions of the gastrointestinal system have been described affecting the entire length of the gut. The lesions show a considerable geographical variation being most common in Japan and the Far East, less common in the Middle East and rare in western Europe. In Japan it is reported that ulcerative lesions of the caecum are characteristic of BS, but these may involve the entire large colon, less frequently the small intestine and occasionally the gastroduodenal mucosa and oesophagus, frequently with vasculopathy histologically [79, 110–113].

Abdominal symptoms are less specific ranging from distension to diarrhoea, and pain with reports of stenosis [114, 115], small and large intestinal perforation [116–118].

**Family History, Epidemiology and Geographical Differences in Prevalence**

Sezer [119] was probably the first to record a family aggregation of the syndrome affecting three brothers. The early reports of a familial incidence of BS were reviewed by Lehner and Barnes [120] who listed reports of 34 families with affected siblings (of both sexes) or parent/child(ren) between 1956 and 1979. Since then this association has been accepted with further similar reports [121]. The association of BS and the
Histocompatibility antigen HLA B5(51) was first recognised by Ohno in 1973 [122]. Since then the genetic linkage in, and the epidemiological basis of, BS has been studied extensively (see chaps. 3 and 14).

Reports of groups of patients with BS from many countries have served to confirm the clinical manifestations of the syndrome. At the same time these reports reveal a considerable variation in the overall prevalence of BS and of its constituent manifestations. Examples of these variations include:

(a) A high prevalence of the syndrome was reported from the Behçet’s Disease Research Committee of Japan in 1977 being 62.7:1,000,000 population with the highest prevalence in the northern island of Hokkaido and lowest in the southern island of Kyushu [79]. Epidemiological surveys from other parts of the world have included Turkey (prevalence = 8–35:10,000) [123], the USA (prevalence = 1:300,000) [124] and the United Kingdom (prevalence = 0.064:10,000 in Yorkshire and 0.03:10,000 in Scotland) [125, 126]. However, only those studies from Japan and Turkey represent formal epidemiological studies.

(b) The manifestations of the syndrome have been shown to differ in frequency in different geographical regions, for example involvement of the gastrointestinal syndrome is maximal in the Far East and rare in western Europe.

(c) The sex ratio also differs geographically, being about equal in Turkey and male predominant in the United Kingdom and Japan. However most studies find that the disease is more severe in male patients and in those with a younger age of onset [127, 128].

(d) The most common age of onset is in the second and third decades of life. However, paediatric cases are well recorded [129–131] although they are uncommon, and onset after the age of 50 is also uncommon [132].

(e) There may be a considerable interval, sometimes many years, between the development of the first manifestation of the syndrome and others which enable a diagnosis to be made [62].

**Aetiopathogenesis**

From the early descriptions of the syndrome there has been debate on its aetiopathogenesis. The early authors, including Behçet himself, concluded that it was of viral aetiology but this was disproved over the years [119, 133–135]. Alternative theories included bacterial infection, mainly streptococcal and exposure to chemicals particularly organophosphates neither of which stood the test of time. Therefore, over the years the theories regarding aetiology have progressed through:

- infective
- exposure to chemicals
- immunological disorder
- autoimmune
- autoinflammatory.
Latterly, it has been shown that this is an immunologically mediated condition, of uncertain aetiology, in genetically susceptible individuals (see chaps. 14 and 15).

**Diagnosis**

From the various clinical manifestation of the syndrome it is evident that the patient may present to one of a number of medical specialities and this has been demonstrated in the literature over the past 70 years. References have already been made in this chapter to authors who are (alphabetically) chest physicians, dermatologists, epidemiologists, gastroenterologists, immunologists, internal medicine physicians, microbiologists, neurologists, ophthalmologists, oral physicians, pathologists, rheumatologists and venereologists to which must be added general practitioners (generalists) and gynaecologists.

In the absence of any specific diagnostic test for BS various physicians with a special interest in the syndrome, therefore, have thought it necessary that schemes, or criteria, for diagnosis should be defined which depend on the grouping together of sufficient features for the physician to be confident of the diagnosis. Several such schemes have been published based on the clinical experience of the authors. There have been three basic forms of such criteria:

- the division of the manifestations of BS as “major” or “minor” (Table 2.2),
- the definition of a “complete” syndrome requiring the presence of three or four of the major manifestations, or “incomplete” requiring three major or two major + two minor manifestations [79, 136, 137],
- spectral involvement dependent on the principal manifestations present, for example mucocutaneous type, mucosal aphthosis, arthritic type, etc. [138, 139].

The first of these diagnostic criteria sets was recommended by Curth in 1946 [140] which required two or more major manifestations for diagnosis. Hewitt and colleagues [141] proposed three major manifestations, being the same three as described by Behçet himself, and recommended that all three were required for a “complete” diagnosis. Only two years later they described the diagnostic importance of skin involvement including skin hyperirritability to needle prick (pathergy test) [142].

The criteria recommended by Mason and Barnes [62], the Behçet’s Disease Research Committee of Japan (1974 and 1987) [79, 136, 137], Hubault and Hamza [143], Ben Ayed and Hamza [144], O’Duffy [145] and Dilşen [146] followed (Table 2.4). The first four of these included the pathergy test as a possible major manifestation which was not included in O’Duffy’s scheme. By contrast Dilşen’s scheme depended on the presence of a positive pathergy test (see above), which he considered a “specific” manifestation, for the diagnosis of what he described as “definite” disease. Ben Ayed and Hamza suggested amendments to these criteria by recommending four major criteria (oral and genital ulceration, inflammatory eye disease being uveitis±hypopyon, and a positive pathergy test) relegating other cutaneous manifestations to the minor category with arthritis and thrombophlebitis.
Table 2.4  Schemes of diagnostic criteria (modified from Br J Rheumatol 1992;31:300, with permission)

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<td>- Folliculitis/acneiform lesions</td>
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<td>- Colitis</td>
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<td><strong>DIAGNOSIS REQUIRES</strong></td>
<td>3 major or 2 major + 2 minor</td>
<td>3 major or 2 major + 2 minor or 2 other major</td>
<td>1 major + 2 minor</td>
<td>2 major or 1 major and 1 minor or pathergy (−) and 3 major or 2 major and 2 minor</td>
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<td>C – 4 major, I – 3 major or 2 other major or 1 major + 2 minor</td>
<td>Oral or genital ulceration + 2 major + 2 minor, 1 major + 2 minor</td>
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</table>

*C* complete form of disease, *I* incomplete form of disease, • manifestations described by authors
BS was being studied in China at about the same time and when there was little communication between Chinese physicians and those in other parts of the world. Our Chinese colleagues also produced diagnostic criteria in which they accepted only three, not four, major features as described by Behçet himself, their scheme otherwise being almost identical to those of Mason and Barnes and from Japan (Table 2.4) [147].

In 1993 Davatchi and colleagues produced Iranian diagnostic criteria, based on their high case load, both in a traditional form and as a “diagnostic tree,” and validated these against a panel of patients derived from several Asian countries [148, 149].

The International Study Group for Behçet’s Disease meanwhile had undertaken an international survey of the incidence of clinical manifestations of BS leading to the formulation of International Criteria [21–23]. This served three purposes:

1. Data regarding the frequency of clinical manifestations was derived from 914 patients from seven countries which were submitted by colleagues experienced in the diagnosis, study and treatment of the syndrome. The specificity and sensitivity of each manifestation was calculated.

2. The performance of the existing schemes of diagnostic criteria in use in 1989 was calculated for sensitivity and specificity. This showed a high specificity (≥90%) for the major manifestations, thrombophlebitis, arterial occlusion and/or aneurysm formation, CNS involvement and epididymitis (100%).

3. A new set of criteria was derived, which required the presence of oral ulcers (present in 98% of patients) as a common clinical feature (Table 2.5). Although these were initially called diagnostic criteria it was rapidly realised that these served as classification criteria. In discussion at the fifth International Conference on Behçet’s Disease, Mayo Clinic, 1989, at which these results were presented it was recorded that “it was recommended that these (criteria) be known as “classification” criteria since they are more useful in ensuring the uniformity of groups of patients for clinical and laboratory studies, and for teaching purposes, than they are for diagnosing the individual case” [23].

This, therefore, follows the pattern of classification criteria for rheumatoid arthritis [150], systemic lupus erythematosus [151], ankylosing spondylitis [152] and osteoarthritis [153].

These criteria (Table 2.5) were further validated by assessing the sensitivity in a new set of 300 patients from seven countries, sensitivity being determined against 62 control patients from China and performed well [154].

In formulating Iranian diagnostic criteria in 1993 further evaluation of the performance of diagnostic criteria schemes was again performed including that of the International Criteria. Although the earlier schemes did not perform as well in that study, it is regrettable that the International Criteria for Classification were included as diagnostic criteria since, as mentioned above, they serve a different function – for the classification of groups of patients and should not be used for the diagnosis of the individual patient [149, 155].
One, therefore, still needs to ask the question “how does one diagnose BS in the individual patient in the routine clinical situation”? The Hippocratic method of grouping together sufficient features to make a diagnosis has always been, and remains, the only way of making a diagnosis. However, the former diagnostic criteria have probably outlived their usefulness as a greater understanding and awareness of the syndrome has developed over the years.

A high “index of suspicion,” and guidelines to diagnosis for the less experienced physician, suggest that a diagnosis of BS should be contemplated when two or three manifestations occur, such as:

- painful recurrent mouth ulcers and genital ulcers, or
- painful recurrent mouth ulcers and an inflamed eye, or
- painful recurrent mouth ulcers, genital ulcers and an inflamed eye, or
- painful recurrent mouth ulcers, genital ulcers and inflamed joints, or
- painful recurrent mouth ulcers, genital ulcers and skin lesions, or
- inflamed eye(s) and joints and skin manifestations, or
- inflamed eye(s), thrombophlebitis and skin manifestations, or
- painful recurrent mouth ulcers, an inflamed eye and a positive family history [156].
This should lead to the referral of the patient to a physician with a greater knowledge and experience of the syndrome. Specialist, or referral, clinics have been developed in those countries where there is a sufficiently high prevalence of the syndrome, such as in Turkey (Istanbul, Ankara), Iran (Tehran) and USA (New York) while in other centres patients are seen in the routine clinics of those physicians with a special interest and experience in the subject.

The same clinical manifestations may also occur in other conditions which, therefore, are included in the differential diagnosis of BS. These include Reiter’s syndrome, seronegative arthropathies, inflammatory bowel disease, sarcoidosis, other vasculitides, multiple sclerosis and pulmonary embolism (Table 2.6) many of which have only been described in detail since 1937 [157].

**Treatment**

The treatment of BS has developed rapidly in recent years. Double blind controlled clinical trials are few and include trials of colchicine [158], and azathioprine [33]. Initial treatments were entirely symptomatic and although these remain important, for example topical steroid applications for ulceration, suppressive treatment for serious eye or vascular involvement includes systemic corticosteroids, immunosuppressive agents and anti-TNFα preparations [41, 159]. This is summarised in Table 2.7.

**Disease or Syndrome?**

The name of the condition has been agreed internationally as being attributed to Behçet. It is recognised that a small minority of our colleagues prefer the addition of the name of Adamantiades who did describe a case before Behçet; but then so did a number of other workers from several different countries. What is more contentious is whether the title should be Behçet’s Disease or Syndrome and it will be seen from the list of references in this book that both titles are in common use and may be considered to be interchangeable. However, what are the reasons behind this difference in nomenclature? The definitions of the words are:

- disease – a disorder of structure or function in a human, animal or plant, especially one that produces specific symptoms or that affects a specific part,
- syndrome – a group of symptoms or signs which consistently occur together.

Those who prefer the title “disease” do so as they regard it as a unified condition – a specific disease – with a wide spectrum of manifestations albeit, at present, of unknown aetiology. Certainly Behçet’s Disease does not fulfil Koch’s postulates. The use of the term Behçet’s Disease was proposed by Lee [160] based on a review of the titles of published works and a survey of the opinions of 22 colleagues.
<table>
<thead>
<tr>
<th>Manifestation</th>
<th>Differential diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouth ulcers</td>
<td>Majority similar to common aphthous ulcers regarding appearance, localization and discomfort/pain; more frequent and frequently multiple; may scar</td>
</tr>
<tr>
<td>Genital ulcers</td>
<td>Majority similar to common aphthous ulcers regarding appearance, localization and discomfort/pain; more frequent and frequently multiple; may scar</td>
</tr>
<tr>
<td>Skin</td>
<td>Majority similar to common aphthous ulcers regarding appearance, localization and discomfort/pain; more frequent and frequently multiple; may scar</td>
</tr>
<tr>
<td>Eyes</td>
<td>Majority similar to common aphthous ulcers regarding appearance, localization and discomfort/pain; more frequent and frequently multiple; may scar</td>
</tr>
<tr>
<td>Joints</td>
<td>Majority similar to common aphthous ulcers regarding appearance, localization and discomfort/pain; more frequent and frequently multiple; may scar</td>
</tr>
<tr>
<td>Peripheral arterial and venous disease</td>
<td>Subclinical peripheral large vein disease uncommon, usually involves large segments with skip areas without embolization; arteritis with occlusion and/or pseudo-aneurysms; microaneurysms of the polyarteritic type very uncommon</td>
</tr>
<tr>
<td>Neurological involvement</td>
<td>Subclinical peripheral large vein disease uncommon, usually involves large segments with skip areas without embolization; arteritis with occlusion and/or pseudo-aneurysms; microaneurysms of the polyarteritic type very uncommon</td>
</tr>
<tr>
<td>Pulmonary involvement</td>
<td>Haemoptysis associated with pulmonary arterial aneurysm; pulmonary artery occlusion; pleural involvement uncommon; interstitial involvement very rare</td>
</tr>
<tr>
<td>Gastrointestinal involvement</td>
<td>Severe abdominal pain; ulcerative lesions at any level but mainly in the ileocaecal region; mild gastrointestinal symptoms should not be associated with Behçet’s syndrome</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>Pericarditis, valve lesions and coronary artery involvement uncommon; rarely intracardiac thrombi</td>
</tr>
</tbody>
</table>
### Table 2.7 Outline of drug treatment of Behçet’s Syndrome (from Rheumatology 2006;45:246, with permission) [159]

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>Mild</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mucocutaneous</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mouth ulceration</td>
<td>Mouth washes</td>
<td>Thalidomide</td>
</tr>
<tr>
<td></td>
<td>Topical steroids</td>
<td>Azathioprine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Infliximab/etanercept</td>
</tr>
<tr>
<td>Genital ulceration</td>
<td>Topical steroids</td>
<td>Colchicine in females</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thalidomide</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Azathioprine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Infliximab</td>
</tr>
<tr>
<td>Erythema nodosum</td>
<td>Colchicine</td>
<td>Corticosteroids</td>
</tr>
<tr>
<td>Acne</td>
<td></td>
<td>Local corticosteroid/antibiotic applications (in combination</td>
</tr>
<tr>
<td>Arthritis/arthralgia</td>
<td>Simple and non-steroidal anti-inflammatory analgesics</td>
<td>Colchicine, corticosteroids, azathioprine, interferon-α</td>
</tr>
<tr>
<td>Ocular involvement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior uveitis</td>
<td>Topical steroids</td>
<td>Azathioprine</td>
</tr>
<tr>
<td>Panuveitis, posterior uveitis</td>
<td></td>
<td>Oral cyclosporine A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Corticosteroids</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Interferon-α</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Infliximab</td>
</tr>
<tr>
<td>Retinal vasculitis</td>
<td>Azathioprine</td>
<td>Oral cyclosporine A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pulsed IV/oral corticosteroids</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Interferon-α</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Infliximab</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>Thrombophlebitis</td>
<td>Symptomatic treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Azathioprine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Low dose aspirin</td>
</tr>
<tr>
<td>Arteritis</td>
<td>Pulsed IV/oral corticosteroids</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pulsed IV/oral cyclophosphamide</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Azathioprine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Infliximab</td>
<td></td>
</tr>
<tr>
<td>Neurological involvement</td>
<td>Dural sinus thrombosis</td>
<td>Corticosteroids</td>
</tr>
<tr>
<td></td>
<td>Parenchymal disease</td>
<td>Pulsed IV cyclophosphamide or oral azathioprine plus pulsed IV/oral corticosteroids</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Infliximab</td>
</tr>
<tr>
<td>Gastrointestinal lesions</td>
<td>Small/large bowel ulceration</td>
<td>Sulphasalazine, azathioprine, infliximab</td>
</tr>
</tbody>
</table>
The latter did reveal a majority (64%) in favour of the title Behçet’s Disease. Lee expressed a concern that even those particularly interested in the condition did not have an agreed diagnostic terminology.

On the other hand, there are many who prefer the term syndrome, at least until even more knowledge has been gained about the aetiopathogenesis, on the basis that one cannot be entirely certain that it is a single disease process. That view was stated in 1979 [120] and even now, 30 years later and with a huge explosion of available research data, this still cannot be answered. The aetiopathogenesis remains unknown, no specific diagnostic test is available, and there is a considerable variation in frequency and prevalence of the syndrome and of its constituent manifestations in different parts of the world. It is not transmissible to unaffected people and, despite the genetic links and familial groupings that have been established, it is not predictable in affected families. Additionally there have been described clusters of associated features – acneiform lesions and arthritis/enthesitis; superficial thrombophlebitis is usually found with large vein thrombosis which clusters with dural vein thrombosis – raising a question of the uniformity of the “disease” [41]. This is not an entirely new concept since Lehner described a “spectral involvement or classification” of BS:

- **Mucosal aphthosis (M-C) type** – oral and genital ulceration ± skin lesions
- **Arthritic type** – joint involvement plus ≥ M-C features
- **Neurological type** – brain involvement plus some or all of the M-C and arthritis features
- **Ocular type** – uveitis plus some or all of the M-C, arthritic and neurological features

Lehner related different immunological findings to the different classification groups, which was before the recognition of a vasculopathy [138, 139, 161].

The terminology currently used by some colleagues – neuro-Behçet, oculo-Behçet, entero-Behçet, vasculo-Behçet – serves to emphasise the principal clinical problem affecting the patient without implying a sub-section of the syndrome.

Thus, the condition is an association of clinical and laboratory manifestations such that the pattern is recognised by experienced physicians as being “Behçet’s Syndrome”.

**International Liaison**

A multidisciplinary International Symposium on Behçet’s Disease was held in Rome in December 1964. Eight papers were presented including a review of the syndrome, the authors and discussants coming from Germany, Italy, Japan, Turkey and the United Kingdom including Sezer [119], Strachan and Wigzell [59] who had contributed to the early literature on the condition. At this meeting Marchionini presented a paper on the “Dermatological View of Morbus Hulusi Behçet” [162]. He reflected that he had been present in Istanbul when “this syndrome was publicly named.” He died before the resulting monograph was published which was dedicated to him [163].
History and Diagnosis

Thirteen years later, as part of the Istanbul Medical Convention, a second International Symposium on Behçet’s Disease was organised by Dilşen at which it was decided to hold a regular series of international conferences the next to be in Tokyo. These were initially held every four years but as the size of these conferences increased, both in terms of the number of participants and abstracts submitted, the interval between conferences was reduced to every three and then two years, and this continues. Proceedings reports of the first to tenth conferences (1964–2002) were published [163–172] but thereafter this was discontinued on the basis that the most important research results were published in peer reviewed journals (Table 2.8).

At the Istanbul Symposium (1977) it was decided to start an International Study Group on Behçet’s Disease members of which were those particularly interested in, and researching into, Behçet’s syndrome. The aim of this group was to maintain communications and contribute to multicentre research. This group continued, being more formally organised after the London conference (1985), intending to be a small number of colleagues working together. However, it became progressively larger as multidisciplinary interest and research developed and an increasing number of colleagues sought membership. Therefore, at the International Conference in Tunis (1996) it was decided to explore the possibility of starting an International Society for Behçet’s Disease (ISBD) to succeed the Study Group and open membership to all who are interested in the syndrome. Further progress was made in Reggio Emilia, Italy (1998) and the society was formally founded at the International Conference in Seoul, Korea, in 2000 its constitutional aim being “to advance the knowledge of the aetiology, pathogenesis, diagnosis, natural history, clinical features, treatment and management of Behçet’s Disease.” The details of the ISBD may be found on its website – http://www.behcet.ws. Every two years, International Conferences continue under the auspices of the ISBD the next being scheduled to be held in London in July 2010.

<table>
<thead>
<tr>
<th>Table 2.8</th>
<th>International conferences on Behçet’s Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>1964 Rome</td>
</tr>
<tr>
<td>2nd</td>
<td>1977 Istanbul</td>
</tr>
<tr>
<td>3rd</td>
<td>1981 Tokyo</td>
</tr>
<tr>
<td>4th</td>
<td>1985 London</td>
</tr>
<tr>
<td>5th</td>
<td>1989 Mayo Clinic, USA</td>
</tr>
<tr>
<td>6th</td>
<td>1993 Paris</td>
</tr>
<tr>
<td>7th</td>
<td>1996 Tunis</td>
</tr>
<tr>
<td>8th</td>
<td>1998 Reggio Emilia, Italy</td>
</tr>
<tr>
<td>9th</td>
<td>2000 Seoul</td>
</tr>
<tr>
<td>10th</td>
<td>2002 Berlin</td>
</tr>
<tr>
<td>11th</td>
<td>2004 Antalya, Turkey</td>
</tr>
<tr>
<td>12th</td>
<td>2006 Lisbon</td>
</tr>
<tr>
<td>13th</td>
<td>2008 Portschach, Austria</td>
</tr>
<tr>
<td>14th</td>
<td>2010 London</td>
</tr>
</tbody>
</table>
At a national level, and in liaison with the ISBD, through national organisations in medical/scientific disciplines (internal medicine, dermatology, rheumatology, ophthalmology, STD clinics, gynaecology, oral medicine, neurology, gastroenterology, immunology, etc.), groups dedicated to Behçet’s Syndrome have been formed in Korea, Japan (governmental) and the United Kingdom (UK Forum on BS).

Similarly patient orientated organisations have been formed in Japan, Turkey, the United Kingdom and the USA and organise their own international conferences alongside the medical/scientific conferences.

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