Rare Diseases of the Immune System
Series Editors: Lorenzo Emmi · Domenico Prisco

Lorenzo Emmi *Editor*

Behçet's Syndrome

From Pathogenesis to Treatment

Springer

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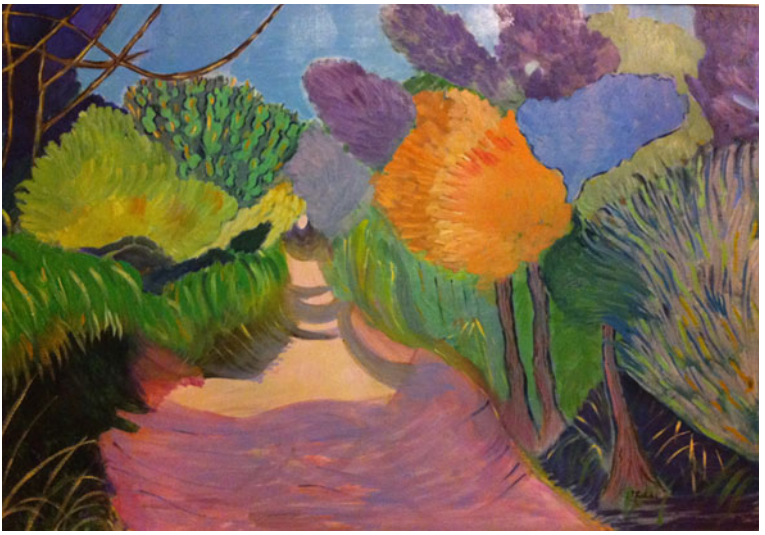

Sentiero
Laura Maddii Emmi
(Private collection)

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Preface 1

About 30 years ago, I started to be in confidence with Behçet syndrome; at that time only a few lines in all the major texts of Internal Medicine were dedicated to this entity, not only in Italy. As I look back to those times when Dr. Ignazio Olivieri and some other friends talked to me, for the first time, about *Behçet Syndrome*, it seems to me extraordinary to be here writing this preface.

In a few years, we have moved from those few lines to write an entire book solely on Behçet with some of the world's leading experts in this field from all the relevant specialties, thus confirming the tremendous growing of knowledge, interest, and the social burden of this disease.

Furthermore in recent years it has become increasingly clear that Behçet is a protean multisystemic disease with some unique features, representing a link between autoimmunity across vasculitis to autoinflammation; moreover Behçet syndrome is perhaps the only disease in which vascular involvement needs immunosuppressive treatments rather than anticoagulation, representing the prototype of inflammation-related thrombosis and our main field of interest in recent years.

My true and deepest gratitude goes to everybody who helped me to realize this work, and especially to Prof. Domenico Prisco, my co-Editor in this important Series of books about the Rare Diseases of the Immune System, and to all the colleagues of the SOD Patologia Medica.

I would like to thanks all the Authors of this book who accepted this challenge.

Moreover a special thanks to Springer Verlag for this exciting opportunity.

I also wish to thank the Italian Behçet Syndrome Association (SIMBA), its President Alessandra Del Bianco, all the members and supporters for their support.

Finally, thanks to all the patients who trust us.

A big thanks also to my dear friends, Gill and Piero, and Cristina, for their precious advice.

Lorenzo Emmi

Preface 2

Thanks to ten Behçet disease patients and also Internet, 7 years ago the Italian Behçet patients Association SIMBA Onlus was established and our dream came true.

Together we share experiences, information about this rare disease, try to overcome loneliness. Our Association has grown in numbers and importance during these years.

SIMBA Onlus focused its efforts especially on reducing the diagnostic delay, which until recently, could even take a few years. Now, we are happy to say that many things have changed, the period taken for diagnosing the symptoms has became a lot shorter, currently we are talking about months. This result makes a big difference for the patients and we are very proud of it.

Moreover we do recognize that much has been done but, of course, there is still always more to do!

Our next goal will be to identify those symptoms *not criteria*, which however are so often reported by the patients with Behcet. It is still very complicated being able to find a specific diagnosis for a rare disease, but we know in what we trust, and we believe that the Association of Patients can really make the difference.

SIMBA Onlus works for an equal access of care for all Italian patients with Behçet disease, therefore our first aim is improving a quality information among patients, families, and doctors, through our website, a group account on facebook, and online newsletters; we also have a representative for each region available to inform about Behçet, its treatment and the reference care centers. Finally, we have contact with all the Behçet's associations worldwide, cooperating for an *esperanto* about this disease.

Another main target is fundraising for our projects and research; in particular SIMBA Onlus supports all the multidisciplinary healthcare projects.

It is very hard to keep an Association alive, but despite everything, despite the disease, we can move forward together, growing up.

Thanks to all those people who support us allowing us to work together every day: because together we can!

Alessandra Del Bianco

Contents

The Numbers of Behçet: A Rare Disease?

1

Agata Polizzi and Domenica Taruscio

In the European Union (EU) countries, a disease is considered rare when it has a low prevalence: i.e. when it affects less than 5 individuals in 10,000. That means which approximately 30 million of people are affected by a rare disease throughout Europe: i.e. from 6 to 8 % of the general European population, on a total number of rare conditions estimated at about 6,000–8,000 [1].

Numbers of Behçet disease (BD) reveals significant regional differences: the disease is more frequent along the Mediterranean, Middle Eastern and Far Eastern areas with its highest prevalence rates in Turkey (e.g. 400:100,000 individuals) where BD cannot be regarded as a rare condition. Conversely, in other European countries (e.g. United Kingdom, Spain, Sweden, or Portugal) the numbers are lower with prevalence rates ranging from 0.3 to 6.4 per 100,000 persons [2, 3]. These figures allow BD to be brought within the definition of a rare condition.

Although rare diseases are very heterogeneous, people with rare conditions share a number of similar experiences despite their different diseases. Overall, a few common key features do exist. More than 80 % of rare diseases are caused by genetic defects, in most cases the onset is in the paediatric age and the natural history is often that of a chronic and disabling condition with a high psychological, social and economic burden affecting the daily life of patients and their families. A multisystem involvement is frequent: the nervous system being most commonly affected. Due to their complexity, a team of interdisciplinary experts is necessary

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in managing and facing all the different aspects of the disease including medical, rehabilitative, psychological, social, basic research and public health problems.

In keeping with the above aspects—which distinguish a rare condition—BD is regarded as a chronic multisystem inflammatory disorder, whose appropriate management requires a multidisciplinary approach. Paediatric cases are rather uncommon. The cause of the disease remains unknown, though an abnormal immune-mediate response along with environmental triggers and a genetic predisposition are involved in the pathogenesis. Overall, the clinical course of BD is considerably disabling as the disease is among the first causes of loss of vision in adulthood. Although therapeutic agents are various, a definite treatment does not yet exist. Thus, the most effective and real management is still dependent upon an early diagnosis, appropriate clinical pathways and focused interventions at follow-up: these contribute to reduce the risk of serious complications and socioeconomic costs related to the disease.

Several relevant issues are still cause of major concerns in the field of rare diseases including BD, such as a high percentage of diagnostic delays, lack of pathogenetic therapies, paucity of drug trials especially for affected children and their equity access, need to prioritise the development of "Orphan drugs", defence of patients rights, creation of registries and bio-banks, difficulties in getting proper financial support for basic and clinical research and, last, scarcity of relevant knowledge and expertise in the specific field.

Far from developing a public health policy specifically aimed to deal with each rare disease, it is worthy to guarantee a global approach considering all rare diseases as a whole [4].

National healthcare centres for surveillance, diagnosis, treatment and rehabilitation of people affected by rare diseases differ significantly across Europe depending on their availability and local organisation. In Italy, for instance, the health policy on rare diseases is regulated by the Ministerial Decree n.279/2001 (www.iss.it/cnmr), which set-up a national network for rare diseases, identified centres of expertise and established the national registry for approximately 500 rare conditions, including BD. In this regard, this system came up to provide a useful data collection for public health initiatives and for stimulating researches on specific rare diseases [5].

At the European level, rare diseases are among the priorities of the EU Public Health Programme 2003–2008 and 2008–2013. In recent years, the adoptions of the documents created by the Commission Communication, the Council Recommendation and the Directive on Cross-border healthcare, contributed to create operational frameworks acting in several areas belonging to rare conditions (e.g. classification and codification, European reference networks, orphan drugs, European committee of experts, etc.) [6–8].

Improving the access of patients with a rare disease to experts care reduces the rate of incorrect diagnosis, delayed diagnosis or misdiagnosis and the use of unnecessary or even harmful therapeutic interventions. Therefore, a network of centres of expertise for rare diseases has been considered an outmost important action at the EU level as also indicated by the EUCERD Recommendations [9].

Through the establishment and evaluation of the European Reference Network on Rare Diseases (RD ERNs), in accordance with the differences in national health care systems and the specificity of various medical areas, recommendations aim to integrate activities among countries as well as to exchange and disseminate information in the field of rare diseases. To ensure interoperability, expected services of the RD ERNs should include disease registries, quality controls for laboratory testing, development of good practice guidelines to get the best standards of diagnosis and care, training and educational programmes, development and adoption of e-tools for tele-expertise and tele-consultation and cross-border assistance procedures [9].

The European Project for Rare Diseases National Plans Development (EUROPLAN—www.europlanproject.eu) is a European initiative, co-funded by the EU Commission (DG-SANCO) and coordinated by the Italian National Centre for Rare Diseases (Istituto Superiore di Sanità) to promote and implement National Plans or Strategies to tackle rare diseases, to share relevant experiences within Countries, to join national efforts with a common strategy at the European level.

In order to raise public awareness on rare diseases, national help lines are currently working altogether at European levels to provide a service of information on rare conditions and related issues (e.g. centres of expertise, exemption for full reimbursement, social care, patients' organisation, psychological support) [10]. In particular, by analysing data collected from the Italian Helpline *Telefono Verde Malattie Rare* at the National Institute of Health (http://www.iss.it/cnmr/telv/index.php?lang=1&tipo=2) BD was recorded among the six most frequent diseases enquired during the last 5 years of activities, out of 16,000 phone calls (unpublished data).

It is only by means of organised and coordinated biomedical information systems (i.e. centre of expertise, registries and data collection) that the number of patients with rare diseases including BD can provide the resources needed for basic and clinical researches, a cornerstone for public health decision-making and a key to achieve a comprehensive collaboration among professional and lay communities.

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From Hippocrates to Hulusi Behçet: What History

2

Donatella Lippi

2.1 Along the Old Silk Road

ἦσαν δὲ καὶ ἄλλοι πυρετοί, περὶ ὧν γεγράψεται. στόματα πολλοῖσιν ἀφθώδεα, ἑλκώδεα. ῥεύματα περὶ αἰδοῖα πολλά, ἑλκώματα, φύματα ἔξωθεν, ἔσωθεν• τὰ περὶ βουβῶνας. ὀφθαλμίαι ὑγραί, μακροχρόνιοι μετὰ πόνων. ἐπιφύσιες βλεφάρων ἔξωθεν, ἔσωθεν, πολλῶν φθείροντα τὰς ὄψιας, ἃ σῦκα ἐπονομάζουσιν. ἐφύετο δὲ καὶ ἐπὶ τῶν ἄλλων ἑλκέων πολλὰ καὶ ἐν αἰδοίοισιν. ἄνθρακες πολλοὶ κατὰ θέρος καὶ ἄλλα, ἃ σὴψ καλεῖται. ἐκθύματα μεγάλα. ἕρπητες πολλοῖσι μεγάλοι [1].

The treatise Epidemics, attributed to *Hippocrates*, consists of seven books which record the observations made by their doctor-authors during the course of their travels as itinerant physicians in northern Greece—Thessaly, Thrace, and the island of Thasos—at the end of the fifth and in the first half of the fourth centuries. Many differences in the texts may reflect the work of different Authors, as well as changes in the thinking of the society as a whole over this period of time and modifications in medical thinking and practice. The title, "Epidemics", may have two different meanings; it could mean either "of the people (demos)", or "sojourning in a place (deme)"; thus its subject could be either the diseases occurring in a given place and time, or the doctor's visits in an area. In addition to the case histories, each book of the Epidemics contains two other types of material: constitutions (accounts of the climatic conditions and the illnesses encountered by the doctor in a particular locality over a specific period of time, usually a year) and

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generalizations (aphorisms, prognostic indications, lists of things to consider, various notes intended for publication, either to students or to the general public). Books I and III of the Epidemics stand out from the other books in their polished form. The case histories of Book III are organized chronologically according to the days of the disease. They consist mostly of lists of symptoms; only rarely is allusion made to treatment, and then only when it elicits symptoms useful in prognosis. In the above-mentioned passage, a very interesting syndrome is described:

> There were other fevers also, which I shall describe in due course. Many had aphthae and sores in the mouth. Fluxes about the genitals were copious ["frequent", "common"]; sores, tumors external and internal; the swellings which appear in the groin ["a curious phrase; I suspect that τα hides a corruption of the text"]. Watery *inflammations* of the eyes, chronic and painful. Growths on the eyelids, external and internal, in many cases destroying the sight, which are called "figs." There were also often *growths* on other sores, particularly in the genitals. Many carbuncles in the summer, and other affections called "rot". Large pustules. Many had large tetters.

When Jones translated this passage, 1868 and later 1923 were running. An earlier English version, published by F. Adams in 1849, included, however, two interesting footnotes [2, 3]:

> But there were also other fevers, as will be described. Many had their mouths affected with aphthous ulcerations. There were also many defluxions about the genital parts, and ulcerations, boils (phymata), externally and internally, about the groins.[1]
>
> *Watery ophthalmies of a chronic character, with pains; fungous excrescences of the eyelids, externally and internally, called fici, which destroyed the sight of many persons.*[2]
> There were fungous growths, in many other instances, on ulcers, especially on those seated on the genital organs. There were many attacks of carbuncle (*anthrax*) through the summer, and other affections, which are called "the putrefaction" (*seps*); also large ecthymata, and large tetters (*herpetes*) in many instances".

Neither Jones' translation nor Adam's assumptions reckoned with clinical conditions of the Behçet syndrome, whose full description dates back to the 1930s of the twentieth century: the first case in contemporary times seems to have been reported by the Greek ophthalmologist Benedict *Adamantiades* in 1931 and the Turkish dermatologist Hulusi Behçet described it independently, for the second time, in 1937, providing a full account of the disease [4, 5].

This double discovery gave raise to a naming confusion, which may create chaos among Behçet patient, too, who already have difficulty in defining their illness [6].

There is in fact serious uncertainty on the naming of this unique disorder, as it often happens using eponyms: eponyms are terms which are named after people (and occasionally places or things), according to an historic-medical approach,

---

[1] "about the groins"—"This description apparently can refer to nothing but pestilential Buboes".

[2] "destroyed the sight of many persons"—"It is impossible not to recognize this as a description of purulent ophthalmia".

dramatically affected by the "primus qui" virus. National pride results in some names prevailing over foreign terminology, causing overlapping descriptions. This has produced a large number of medical eponyms, which may lead to confusion owing to their inconsistent application between countries and medical specialties. There are hundreds of eponymous medical syndromes and signs, often with fantastic double barreled names: this is the case of the *Adamantiades-Behçet syndrome*. The most important proceeding about the name of the disease was first held in the International Congress of Dermatology, in Geneva, in September 1947, when the disease, which occurred with oral and genital periodic ulcers, was named as "morbus Behçet" (Behçet disease) [7].

2.2 A Tricky Syndrome

Before 1937, many diseases were described which could fit Behçet's Syndrome.

Table 2.1 shows the list provided by Barnes [8]: regardless of its incompleteness, it is a functional tool, to provide a general glance on the disease's description's steps.

From this synopsis, it appears that most of the scholars who dealt with a possible Behçet's Syndrome were ophthalmologists or dermatologists, as the most striking symptoms include recurring ocular involvement (*hypopyon iritis*), scrotal ulcerations, aphtous stomatitis, and relapsing skin manifestations (*pyodermitis*) [9–12].

This list, however, could be extended, adding other examples dating back to more distant times: in 1772, for instance, Janin [13] reported the case of a male patient with recurrent hypopyion iritis, which is considered a major criterion in defining the disease [14]: in 1895, both Neumann from Vienna [15] and Christlieb from Würzburg [16] described the cases of female patients with recurrent orogenital aphtous ulcerations.

Table 2.1 Barnes general glance on the descriptions of the disease

Speciality	Authors	Country	Year
Ophthalmology	Gilbert	Germany	1920
	Shigeta	Japan	1924
	Fuchs	Austria	1926
	Adamantiades	Greece	1931
	Dascolopoulos	Greece	1932
Internal medicine	Chauffard et al.	France	1923
Dermatology	Neumann	Germany	1894
	Planner and Remenovsky	Germany	1923
	Lipschutz	Austria	1924
	Whitwell	United Kingdom	1934

Source: Barnes CG (2010) History and diagnosis In: Yazici Y, Yazici H (eds) Behet's syndrome. Springer, Berlin Heidelberg New York, pp. 7–34

These observations were followed in 1906 by the German scholar Reis, who reported the association among "relapsing ocular inflammation", cutaneous lesions (*erythema nodosum*), and arthritis [17].

In 1908, Blüthe [18] recorded the same symptoms' group formed by "relapsing hypopyon-iridocyclitis", *mucocutaneous* lesions and arthritis with histological evidences of uveitis and optic nerve atrophy.

Between 1920 and 1925, Gilbert published the cases of patients, suffering from recurrent hypopyon iridocyclitis, recurrent arthritis, and skin lesions [19–22], while Planner and Remenowsky [23] reported a case with iritis and genital lesions and Weve [24] published a case with recurrent hypopyon iridocyclitis, arthritis, mucocutaneous lesions, periodontitis, and neurologic findings, once more of exactly the same symptom constellation.

The clues multiplied, decidedly pointing to the Far East, where, in the past, the trail from China to the West was opened, and developed into the *Silk Road*.

In Japan, in fact, Shigeta [25] reported the case of a man with recurrent mucocutaneous ulcers and hypopyon iritis with histological detection of uveitis and optic nerve atrophy.

In the same period, Pils [26] published a case with mucocutaneous lesions, thrombophlebitis, and arthralgia: Grütz [27] and Carol and Ruys [28] treated two patients with recurrent genital lesions and arthralgia.

Samek and Fisher [29] are supposed to be the first ones to use the *pathergy test*: they reported a case with periodic mucocutaneous lesions and erythema nodosum.

Recurrent mucocutaneous lesions with histologically demonstrated leukocytoclastic vasculitis in a genital ulcer and a skin lesion were referred by Walter and Roman [30], at the same time as Kumer [31] reported mucocutaneous lesions in women with a histologic detection of leukocytoclastic vasculitis in a genital ulcer and an erythema nodosum lesion with some CNS signs.

In all these cases, however, the symptoms or signs were attributes either to another disease such as, for instance, septic metastasis [19–22], tuberculosis [32], and focal bacterial infection or allergy [24] or to a coincidence, and none of them indicated "a new or a single syndrome" with "classical triad" consisting of the *triple symptom complex* [33].

2.3 The Greek Benedictos Adamantiades

In the following period, the first attempt to consider this complex as the expression of a defined disease, was made by the Greek ophthalmologist Benedictos Adamantiades: he reported a 20-year-old male patient with recurrent hypopyon iritis, mucocutaneous symptoms, and arthritis [34, 35], underlining that "recurrent hypopyon iritis" represents itself a distinct clinical entity. However, "relapsing ocular lesions" may occur also in various infectious or non-infectious systemic disorders, such as tuberculosis, syphilis, leprosy, various vasculitides, including Vogt-Koyanagi-Harada syndrome and some other endogenous uveitis, as well as

staphylococcal bacteremia, sepsis, or local bacterial infection, as some of the etiological factors [36–38].

That is why Adamantiades attributed the disease to *bacterial staphylococcal infection* and focal illness, and referred to similar cases, reported by Reis [17], Gilbert [19–22] and Weve [24] who also ascribed the disease to those etiologies. Before the important publications of Hulusi Behçet, numerous other articles were published about the same group of symptoms or signs [39–51] and the naming problem started [52]. Simplicity is never very likely in the cobweb of events and it is anti-historic to identify the "primus qui": in demythicizing the concept of the uniqueness of the scientific "discovery", any finding must be envisaged as the point of convergence of the efforts of a whole scientific community, but, in this case, it must be accepted that Adamantiades was not the first to describe the manifestations of the disease and, above all, he did not suggest the concept of "triple symptom complex", eluding the true nature of the disease, which was not considered as a distinct entity until Behçet's studies [33, 52, 53].

2.4 The Turkish Hulusi Behçet

Jensen from Denmark first used the eponym "Behçet" in the title of the chapter to describe the "triple symptom complex" of Behçet consisting of "oculo-oromucocutaneous" manifestations [54, 55].

Behçet was in fact the first one who recognized a group of characteristic symptoms and signs and collected all the manifestations (recurrent oral aphthae, genital ulcerations, recurrent hypopyon uveitis) into a single disease [56–58], providing evidence of it.

Hulusi Behçet was born in Istanbul on February 20, 1889: he was the son of Ahmet Behçet, the superintendent of schools: he attended the elementary school in a French school in Beyrut. In 1901, he started his education in Kuleli Military Medical School, and he graduated in 1910. He worked as an assistant in the dermatology department of Gülhane Military Hospital with renowned professors, such as Eqsref Ruqsen, Talat Çamlž, and Resat Ržza. In 1914, he was assigned to the position of vice chief of staff of Kžrklareli Military Hospital. He worked as a consultant dermatologist in the Edirne Military Hospital until 1918, when he started working as a voluntary assistant of Blumenthal and Cherevsesky in the Charité Hospital, department of dermatology and syphilis, first in Budapest and then in Berlin. In 1919, he returned to Turkey and worked as a private dermatologist: he was assigned to the position of chief of staff of the Hasköy Venereal Diseases Hospital in 1923. After 6 months, he moved to Istanbul Vakžf Guraba Hospital and in 1933 he became a professor and director of the Istanbul University department of dermatology and venereal diseases. Hulusi Behçet, who received the title of distinguished professor in 1939, died of a heart disease in 1948, at the age of 59, forever linking his name to the *tri-symptom complex* [59–61].

In fact, the disease, currently known all over the world as "Behçet disease", "Behçet syndrome", "*Behçet's triad*", "Tri-symptom Behçet", "La maladie de Behçet", or "Morbus Behçet", was first supposed by Hulusi Behçet since 1924: the story deals with a patient, who had been examined because of eye disturbances, recurrent oral and genital ulcers for 40 years, receiving several different diagnoses. Some doctors thought of tuberculosis or syphilis, while some other doctors said a microorganism which was not present in Europe might have caused the disease. Hulusi Behçet, who continued to examine the patient after his loss of vision, thought that the causative agent was a virus [62]. In 1930, a woman patient presented with oral and genital ulcers and eye redness: Behçet, who followed-up the patient until 1935, could not get any specific results, although he searched for tuberculosis, fungus, syphilis, and other disease agents and he biopsied. Another male patient, having applied to a dentist because of deep oral ulcers in 1936, was sent to Behçet, who recognized the same symptoms seen in the previous patients. Behçet did not manage to get a specific diagnosis in spite of all his examinations, thus deducing that the causative agent was a *virus*. He started his studies on viruses with the support of Hugo Braun, who was researching in microbiology at that time in Turkey. Meanwhile, Niyazi Ismet Gözcü, who was chief of the Gülhane Hospital, reported another patient with primarily eye symptoms to Behçet. When Erich Frank, a German doctor working in Turkey, reported another patient who showed all of the symptoms, the number of patients reported from Turkey reached five [33].

Behçet, as a dermatologist, gave great significance to the recurrent oral ulcerations (aphthosis) which are considered today the "universal hallmark" and the only *sine qua non* symptom of this disorder [33]. He published his observations in a six-pages article in German, providing very interesting pictures: he related his disappointment in obtaining definite results from his histological tests ("negative Ergebnisse"), listing the unsuccessful efforts to detect the virus he supposed responsible for the disease ("saprophytische Virusarten") [5].

This first publication was followed by other studies, where he undoubtedly indicated a strong association of three unrelated manifestations together: "transient aphtous changes in the mouth", "ulcerations on the genitalia", possible "attacks of iritis"[57, 58]. He was aware that these symptoms could simulate other diseases, but his more than 20-year-long experience provided him with the confidence that he was facing a "separate disease" [58]. On the ground of his own observations, he became convinced that the sets of symptoms were "differently localised manifestations of one and the same disease" and he blamed dermatologists ad ophthalmologists for not having recognized the disease, due to the ignorance of each other's reports [58]. Behçet at this stage of his research thought that the disease depended on a "virus infection", but he left himself a way of escape, wishing not to be "dogmatic about this possibility", stressing "the need for further research on this point" [58].

Subsequently, other cases were reported and again the eponym "Behçet syndrome" started to be accepted as an identification mark of this pathological entity.

After the publication of other papers and case reports, the whole world at long last accepted that they had to face a separate disease entity. During the International Medical Congress of Geneva, in 1947, the international society together

honored the first describer of "Tri-Symptomenkomplex/Triple Symptom Complex" and, therefore, named the disease "Morbus Behçet" consisting of the "Classical Triad". Behçet Disease has been called with various names in the literature from yesterday to today, as shown by Table 2.2 [61], but, according to some authors [33], the double eponym Adamantiades-Behçet must be rejected, as Adamantiades, as an ophthalmologist, was too persuaded of the importance of the

Table 2.2 Various names of Behcet Disease

Name of the disease	Author	Reference
Triple symptom complex	Behçet H	Some observation on the clinical picture of the so-called triple symptom complex. Dermatologica 1940; 81:73–83
Syndrome de Behçet	Jensen T	Sur les ulcerations aphteuses de la muqueues de la bouche et de la peau genitale combiness avec les semptomes oculaises (Syndrome Behçet). Acta Derm Venereol 1941; 22:64–79
Behçet's disease	Sezer FN	The isolation of virus as the cause of Behçet's disease. Am J. Ophtalmol 1953; 36:301–15
Adamantiades-Behçet's symptom complex	Bouzas A	The Adamantiades-Behçet's syndrome. Bull Soe Helen Ophtalmol 1956; 24:41
Behçet's multiple symptom complex	Strachan RW, Wigzell FW	Polyarthritis in Behçet's multiple symptom complex. Ann Rheum Dis 1963; 22:26–35
Mucocutaneus-ocular syndrome	Robinson HMJ, Mc Crumb FRJ	Comparative anlaysis of the mucocutaneus ocular syndrome: report of 11 cases and review of the literature. Arch Dermatol Syphil. 1960;61:539
Magic syndrome	Frestein GS, Gruber HE, Weisman MH, Zvaifler NJ, Barber J, O'Duffy JD	Mouth and genital ulcers with inflamed cartilage: Magic syndrome. Five patients with features of relapsing policondritis and Behçet's disease. Am J Med 1985; 79:65–72
Pseudo-Behçet's syndrome	Levine JA, O'Duffy JD	Pseudo-Behçet's syndrome a description of 23 cases. In: Godeau P, Wechsler B (eds) Behçet's Disease, Proceedings of the Sixth International Conference on Behçet's Disease. Paris 30 June to 1 July 1993: Elsevier Sci Pub, Amsterdam, 1993: 295–298

Source: Demirhan EA, Öncel Ö (2006) Prof. Dr. Hulusi Behçet (A Famous Turkish Physician) (1889–1948) and Behçet's disease from the point of view of the history of medicine and some results. 21st Congress of the British society for the history of medicine. 1–4 September 2005, UK-Exeter. JISHIM 5(10):51–63

"recurrent ocular lesions", that he went on publishing more and more papers on the same subject, even after the worldwide recognition and acceptance of the disease as "Morbus Behçet" in 1947: ocular problems in fact, occur in approximately half of Behçet patients and the diagnosis of Behçet disease can still be made, even if such an ocular involvement is missing [33]. The eponym, however, is not the sole problem: there is still a debate on which terminology, Behçet's syndrome (BS) or Behçet's disease (BD), is preferable: as a matter of fact, the lack of a known pathogenesis or a definitive diagnostic test, and the variability in prevalence and incidence of the condition and its constituent manifestations, suggest that the terminology Behçet's syndrome is preferable.

2.5 Come Back to the Future

The distribution of Behçet's disease in countries between the Mediterranean and the Orient, and its virtual absence in indigenous Amerindians and among populations south of the equator is intriguing [62].

Early trade routes between the Mediterranean and the Orient (the Silk Roads) promoted both commerce and the spread of disease, but although this ubiquitous disorder exhibits a distinct geographic variation and is endemically higher particularly in Turkey, Asians, and Japan, such a migration pattern, that the prevalence of Behçet disease is increasing in Western countries due to migration patterns, has never been demonstrated for this disorder up to now [33].

Since Hippocrates, no further descriptions emerge in the literature for many centuries, but in the last 20 years a striking increase in reporting has occurred across southern Europe, Eurasia, and the Arabic world: is there a reporting bias as the distinction between Behçet's disease and both syphilis and tuberculosis became appreciated? This trisymptom complex (hypopyon, iritis, and orogenital aphthous) in fact was considered to be a manifestation of syphilis till 1937, when Behçet proposed a separate disease entity.

Otherwise, is the rise in incidence real, as the result of contributory *environmental agent(s)*, as both, Behçet and Adamantiades, suspected?

However, numerous interdependent and independent *genetic* regions may influence the disease, and their explanation may have important implications for the management of patients with Behçet's disease, providing grounds for new forms of immunomodulation and increasing the possibility of early diagnosis in such a disabling disease.

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Epidemiology of Behçet Syndrome

3

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Behçet's disease (BD) is a systemic inflammatory disease typically characterized by oral and genital ulcers and variable manifestations affecting other organs, mainly skin and eye. Published epidemiologic studies on BD are difficult to compare because of different study designs, settings, and methods. In particular, the lack of universally accepted classification criteria has hampered a reliable definition of prevalence and incidence rates of BD in different populations. In fact, 16 different sets of classification/diagnosis criteria have been published so far [1]. The publication of the International Study Group for Behçet Disease (ISG) criteria has somewhat obviated this limitation, since these criteria have gained widespread acceptance and are in fact those most commonly used in clinical studies [2, 3]. However, these criteria tend to perform poorly in patients with recent onset of BD because of poor sensitivity, which limits their usefulness in this subset of subjects [4]. The International Criteria of Behçet's Disease (ICBD) have subsequently been proposed to attain a higher sensitivity [2–4]. Estimates of sensitivity and specificity of the ICBD criteria in the original study were 94 (ISGB 81 %) and 90.5 % (ISGB 96 %). The International Criteria for Behçet's Disease (ICBD): a collaborative study of 27 countries on the sensitivity and specificity of the new criteria

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[5]. However, these criteria remain to be validated in different populations before they can reliably be used in epidemiological studies. Table 3.1 summarizes the sensitivity and specificity of these classification criteria.

Another problem that compounds epidemiological research is the variability in the methodology employed in clinical studies (registries, hospital records, district databases). Most published studies are retrospective in nature, while there is a

Table 3.1 Sensitivity and specificity of classification criteria for Behçet's disease

Study	Reference	Number	Criteria	Sensitivity (%)	Specificity (%)
ISG 1990	[2]	886	ISG	92	97
			ICBD	–	–
Iran 1993	[6, 7]	2069	ISG	86.2	97.5
			ICBD	–	–
APLAR 1998	[8]	216	ISG	72.2	99.3
			ICBD	–	–
Russia 2000	[9]	105	ISG	79.8	99.8
			ICBD	–	–
USA 2000	[10]	164	ISG	75.6	–
			ICBD	–	–
India 2004	[11]	50	ISG	72	–
			ICBD	–	–
Singapore 2004	[11]	37	ISG	46	–
			ICBD	–	–
China 2004	[11]	98	ISG	81	–
			ICBD	–	–
Korea 2004	[11]	1454	ISG	58	–
			ICBD	–	–
Iran 2004	[11]	4900	ISG	82	–
			ICBD	–	–
ICBD 2006	[12–14]	2556	ISG	82.4	96
			ICBD	96.1	88.7
Germany 2008	[15]	86	ISG	83.7	89.5
			ICBD	96.5	73.7
China 2008	[16]	322	ISG	64.5	99.2
			ICBD	87	94.1
IRAN 2010	[17]	6128	ISG	78.1	98.8
			ICBD	98.2	95.6

paucity of true population-based studies; moreover, some studies do not mention prevalence and incidence rates [18, 19].

Despite these limitations, consistent data point to higher incidence and prevalence rates of BD along the ancient Silk Road (stretching from the Middle Est to the Far East and Mediterranean Countries) compared to a lower prevalence in Northern European Countries and United States [20]. The highest frequency of BD has been reported in a population-based study in Turkey with a prevalence of 370 cases per 100,000 people [21]. In Italy, two population-based studies have estimated the prevalence of BD to be 3.8/100,000 in Reggio Emilia and its province [22] and 9/100,000 in the Southern Italian region of Basilicata [23], consistent with the notion that BD in Europe clusters around Mediterranean countries. It is unclear whether the disparities observed in the frequency of BD in different countries are due to genetic or environmental factors. A study that specifically investigated this issue revealed that the risk of developing BD was significantly higher in Turkish immigrants to Germany than in German subjects, although it remained below the reported risk in Turkey [24]. These data suggest that an interplay of genetic and environmental factors is actually involved in determining the susceptibility to BD. The impact of the genetic make-up has also been demonstrated by studies conducted in twins [25], which have shown higher concordance rates for BD in monozygotic compared with dizygotic twins.

Among the alleles investigated, the HLA antigen B51 has been shown to be more prevalent in patients with BD relative to unaffected subjects. However, the association between BD and HLA-B51 is not very tight [26], and the contribution of HLA-B51 to the overall genetic BD susceptibility has been estimated not to exceed 20 % [27]. More specifically, in a meta-analysis of 4,800 patients with BD and 16,289 controls, the pooled odds ratio of the risk of developing BD conferred by the HLA-B51 allele was 5.78 (95 % CI 5.00–6.67). Among the HLA-B51 subtypes, HLA-B5101 has emerged as the main risk factor, whereas HLA-B5107 might be negatively associated with BD [28]. It remains debated whether the HLA-B51 allele is linked to specific disease manifestations or disease severity [29, 30].

BD usually develops in subjects in the third decade of life, but early and late onsets have also been reported [31]. A higher frequency of severe lesions, including inflammatory ocular manifestations, has been noticed in younger patients, particularly males [32]. The male to female ratio varies in different countries, ranging from 5.37 to 1 (Egypt) to 0.38 to 1 (US) [33]. Familial clustering is rare in Europe, but has been described in up to 18 % of Turkish and 15 % of Korean patients with BD [34–37].

The most significant studies published about epidemiological data are reported in Table 3.2.

Table 3.2 Most significant studies published about epidemiological data in Behçet's disease

Country	Type of study	Year(s)	Method	Criteria	Annual incidence cases/10^5/year	Prevalence cases/ 100,000	Ref.
German	Retrospective/prospective population based	1984–1997	German registry of Adamantiades–Behçet's disease	ISG for BD		1.68 (1989) 2.26 (1994)	[24]
USA	Retrospective population based	1960–2005	Hospital records	ISG	0.38	5.2	[38]
Northern Italy	Retrospective population based	1988–2004	District database for rare diseases records	ISG	0.24	3,8	[22]
North of Israel	Retrospective hospital based	2007–2008	General practitioners interviews	ISG		50	[39]
Center of Israel	Population based	?–2002	General practitioners database: questionnaires, interviews and clinical examinations	ISG		120	[40]
France	Cross-sectional prevalence study population based	2003	Medical records	ISG		7.1	[41]
Portugal	Retrospective	1990	Medical records	Mason and Barne's		1.5	[42]
Sweden	Population based	2011	Clinical records	ISG		4.9	[43]
UK (Yorkshire)	Prospective population based	1977	Questionnaire moll	Mason and Barne's		0.64	[44]
Iran	Prospective study population based	2004–2005	Questionnaires, interviews and clinical examinations			80	[45]
Turkey	Field survey		Questionaires, interviews, clinical examinations			370	[46]

(continued)

Table 3.2 (continued)

Country	Type of study	Year(s)	Method	Criteria	Annual incidence cases/10^5/year	Prevalence cases/ 100,000	Ref.
Turkey							
Japan	Nationwide epidemiological survey	1991	Questionnaires sent to hospital selected patients	ICBD	Not described	Not described	[47]
China	Hospital-based study	1978–2000	Datasheets	ISG	Not described	2.62	[48]
Korea	Retrospective hospital based	1997–1999	Hospital records	ISG Shimizu's	/	/	[18]
German	Registry hospital based	1961–2005	Hospital and private clinics records	ISG	4.16 (Past 10 years) 1.0 (actual)	/	[49]
Turkey	Retrospective population based			ISG	80–420	/	[19]

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Behçet's Syndrome According to Classical and Population Genetics

4

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4.1 Introduction

The etiology of Behçet's disease (BD) remains unclear. However, as in many other inflammatory and/or immune-centered diseases, environmental factors are thought to trigger the symptomatology in individuals that harbor a particular genetic background. The strong association between BD and the human leukocyte antigen (HLA) class I allele, *HLA-B*51*, has been well established. This association indicates that the *HLA-B*51* allele is one of the genetic factors underlying BD. Still, the presence of *HLA-B*51*-negative BD patients suggests that other genetic

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factor(s) and/or various environmental or infectious agent(s) might also be risk factors for the development of BD. With the exception of the *HLA-B*51* allele, the molecular nature of the "genetic background" of BD has, until recently, remained mostly unknown. Novel candidate genes for BD are now being identified, with marked improvement in genetic analysis technology. This chapter describes classically known and recent genetic findings, as well as their possible involvement in the pathogenesis of BD.

4.2 HLA-B*51

HLA, located on chromosome 6p21.3, is the major histocompatibility complex in humans. HLA encodes genes involved in antigen processing and the presentation of antigenic peptides to T cells, and is instrumental in many innate and adaptive immune responses. Peptide binding to HLA molecules is the single most selective step in the recognition of pathogens by the adaptive immune system, and depends on specific amino acids in the peptide-binding groove of each HLA allele. The HLA genes are the most polymorphic ones in the human genome, and the alleles of the HLA genes vary widely among individuals. In addition, the distribution of HLA alleles varies widely according to ethnicity and geographic area. Therefore, variability in HLA allele types can lead to differences among individuals/ethnic groups regarding susceptibility to or protection from many diseases.

The HLA class I molecule *HLA-B*51* allele is strongly associated with BD in many different ethnic groups [1–4]. The allele frequency of *HLA-B*51* is markedly increased in BD patients compared with controls, while *HLA-B*52*, which is identical to *HLA-B*51* except for two amino acid residues, is not associated with BD. Therefore, it is assumed that the immune response against the specific peptides that bind to two *HLA-B*51*-specific amino acids contributes directly to the development of BD [5]. The HLA class I molecules bind peptides derived from endogenous proteins of host or pathogen origin and present them to $CD8^+$ cells. The characteristics of the peptide-binding motifs of *HLA-B*51* have already been reported (http://www.syfpeithi.de/); however, HLA-B51-restricted causative antigens for BD remain unclear, and thus further studies are needed to clarify the HLA-B51-driven immune response in the pathogenesis of BD.

BD exists worldwide but is clearly more prevalent in countries along the ancient Silk Route, which spans from East Asia to the Middle East and the Mediterranean basin [2, 6]. *HLA-B*51* is the most strongly associated risk factor for BD in these areas [2, 3]. In the Silk Route areas, BD has a prevalence ranging from 10 to 420 cases per 100,000 individuals; in contrast, it is rare in Western and Northern Europe and the United States (U.S.), accounting for less than 1 case per 100,000 individuals [6–8]. The frequency of the *HLA-B*51* allele is lower in general European and U.S. populations than in populations in the Silk Route areas, suggesting that the regional difference of *HLA-B*51* frequency reflects regional differences in the prevalence of BD. Although the frequency of *HLA-B*51* in

Italian, Portuguese, Alaskan Eskimo, and Canadian Inuit populations is similar to the frequency in the Silk Route areas, the prevalence of BD is only about 2 cases per 100,000 individuals in Italian and Portuguese populations, and no cases have ever been reported among Eskimo or Inuit populations [6]. In addition, BD has never been reported in U.S.-residing Japanese-Americans even though Japanese-Americans share the same genetic background as native Japanese, in whom the prevalence of BD is 13.5 cases per 100,000 individuals [6, 9, 10]. This fact implies that environmental factor(s) that interact with *HLA-B*51* and specifically distribute in the Silk Route areas are responsible for the development of BD.

More recently, Hughes et al. performed dense genotyping in the HLA region to locate the genetic association between *HLA-B*51* and BD [11]. They have shown that the genetic association between *HLA-B*51* and BD disappears completely in Turkish and Italian populations after controlling for the effect of rs116799036 (which is located in the approximately 24 kb upstream promoter region of *HLA-B*). Therefore, they have suggested that the risk previously ascribed to *HLA-B*51* is likely not causal with respect to BD. Further analysis is required to confirm their findings, with due consideration given to the extensive genetic diversity and the strong linkage disequilibrium in the HLA region.

4.3 Possible Non-HLA Candidate Genes

The *HLA-B*51* allele is the major susceptibility gene responsible for BD. In many ethnic groups, approximately 50–80 % of BD patients possess the *HLA-B*51* allele [3]. Hence, about 20–50 % of BD patients lack the *HLA-B*51* allele, suggesting that other genetic and/or environmental factor(s) might also be risk factors for the development of BD. To identify novel susceptibility genes for BD outside HLA, many candidate gene investigations based on plausible biological functions related to the disease pathogenesis have been performed. Possible susceptibility genes for BD in the non-HLA region that have been identified by candidate gene approaches include *ICAM1*, *coagulation factor V*, *VEGF*, and *eNOS*.

4.3.1 ICAM1

Intercellular adhesion molecule-1 (ICAM-1), a cell-adhesion molecule that regulates cell–cell interactions in the immune system, is mainly expressed on endothelial cells. ICAM-1 is involved in the T-cell activation and the transendothelial migration of neutrophils [12]. ICAM-1 expression is increased during inflammation, and elevated serum levels of soluble ICAM-1 are observed in patients with active BD [13, 14]. These facts suggest that ICAM-1 plays an important role in the induction and development of inflammation in BD. Previous studies have reported the association of *ICAM1* polymorphisms with BD. The lysine to glutamic acid variation of codon 469 (K469E) is associated with an increased risk of BD in Palestinian, Jordanian, Korean, and Lebanese populations [15–17]; in contrast, the

allele frequency of the glycine to arginine allele of codon 241 (G241R), but not E469, was significantly higher in the Italian population [18]. The E469 allele has also been associated with clinical manifestations of BD in Korean and Tunisian populations [16, 19].

4.3.2 Coagulation Factor V

BD is a systemic inflammatory disease that carries a high risk of venous thrombosis (the formation of a thrombus within a vein). BD confers a 14-fold relative risk of developing venous thrombosis compared with BD-free controls [20]. A G-to-A substitution at nucleotide +1691 of the *coagulation factor V* gene (+1691 G/A), called factor V Leiden mutation, is one of the most prevalent genetic risk factors for venous thrombosis [21, 22]. A recent meta-analysis [23] that includes 27 previous studies assessing the association of BD with possible genetic risk factors for venous thrombosis in BD patients demonstrated that factor V Leiden is significantly associated with BD and the presence of thrombosis. Importantly, these results were only relevant in Turkish patients with BD, suggesting that this mutation might contribute to venous thrombosis in at least Turkish BD population, but not in all populations. Meanwhile, the meta-analysis revealed no significant association between other factors (+20210 G/A in the prothrombin gene and 677 C/T in the methyltetrahydrofolate reductase gene) and thrombosis in the context of BD.

4.3.3 VEGF

Vascular endothelial growth factor (VEGF) is a potent endothelial-cell-specific mitogen and permeability factor with key roles in angiogenesis, vascular maintenance, and inflammation [24–27]. VEGF augments interferon-γ and inhibits interleukin (IL)-10 secretion by T cells responding to mitogens or antigens; thus, VEGF can enhance a Th1 phenotype [28], which is evident in patients with active BD [29, 30]. Increased serum VEGF concentrations have been observed in patients with BD, and patients with active disease have significantly higher VEGF levels than patients with inactive disease [31]. In addition, ocular BD patients exhibit higher VEGF levels than non-ocular patients [31]. Therefore, VEGF may participate in the course of BD, especially during the active stage, and increased serum VEGF concentrations may be a risk factor for the development of ocular disease. The *VEGF* promoter polymorphisms −634C (the C allele of −634 C/G) and −2549I (an 18-bp insertion at −2549) are reportedly associated with BD susceptibility in the Italian population [32]. Moreover, −634C and −2549I have been involved in the development of ocular inflammation of BD in Korean and Tunisian populations, respectively, but demonstrated no association with disease susceptibility [33, 34].

4.3.4 eNOS

Nitric oxide (NO), which is mainly produced in endothelial cells, plays an important role in regulating vascular homeostasis and contributes to vascular dilation, inhibition of platelet agglutination and cell-adhesion molecule expression, and vascular smooth muscle relaxation [35]. NO concentration is reportedly decreased in BD patients during the active period of the disease [36], suggesting that the decreased NO level may be centrally involved in endothelial dysfunction and thrombosis in BD patients. NO is synthesized from L-arginine by at least three distinct isoforms of the enzyme NO synthase (NOS). Three isoforms of NOS identified so far are NOS1 (neuronal NOS), NOS2 (inducible NOS), and NOS3 (endothelial NOS, or eNOS) [37]. Of these, eNOS is mainly expressed in the endothelial cells and contributes to the inhibition of platelet and leukocyte adhesion, inhibition of the proliferation and migration of vascular smooth muscle cells, and vascular dilation [35]. Several studies have been performed to assess the association between *eNOS* gene polymorphisms (+894 G/T and a 27-bp tandem repeat in intron 4) and BD; some, but not all, have reported that these polymorphisms are associated with BD [38]. A recent meta-analysis that includes these previous studies [38] has suggested that these polymorphisms do not confer susceptibility to BD in Turkish or Asian populations. Moreover, the meta-analysis also demonstrated that +894 G/T revealed a significant association with BD in European and Tunisian populations, while the risk allele of +894 G/T differed between these populations: the T allele was associated with increased disease risk in Europeans and decreased risk in Tunisians. There is still no clear explanation for this controversial result.

Although these four genes might indeed be susceptibility genes for BD, the genetic contributions of these genes to BD remain unclear. Most of the previously reported candidate gene approaches for BD were characterized by low statistical power because of small sample sizes and might therefore lead to false positive or false negative results. Aside from *HLA-B*51*, genetic factors with small or moderate effects appear to be involved in the risk of developing BD. To overcome this issue, large sample sizes (which usually allow even small effects to be statistically significant) would be required.

4.4 Genome-Wide Association Study Findings

A genome-wide association study (GWAS) is an approach that involves rapidly genotyping a dense panel of genetic markers that covers the entire genome and has great power to detect genetic variants that contribute to the risk of developing common and complex diseases. BD susceptibility genes/loci that have been successfully identified by GWASs include *HLA-A*26*, *IL10*, *IL23R-IL12RB2*, *STAT4*, *ERAP1*, *CCR1-CCR3*.

4.4.1 HLA-A*26

A GWAS of BD that employed 23,465 microsatellite markers was published in 2009 [39]. This GWAS identified one marker in the HLA class I region that is not in linkage disequilibrium with *HLA-B*51*. A comprehensive analysis of the HLA class I region found that the *HLA-A*26* allele was significantly associated with BD independently of *HLA-B*51*, suggesting that *HLA-A*26* is the second major susceptibility allele for BD. Individuals with *HLA-B*51*, *HLA-A*26*, or both account for approximately 80 % of all BD patients in Japan. The association of BD with *HLA-A*26* has also been reported in Taiwan, Greece, and Korea [40–42]. In addition, it has been reported that the phenotype frequency of *HLA-A*26* was increased ~7-fold in Saudi Arabian patients compared with healthy controls; however, this difference was not statistically significant [43]. Moreover, it has been suggested that *HLA-A*2601*, one of the major *HLA-A*26* subtypes, might be associated with ocular BD in the Japanese population and might also be a marker for poor visual prognosis [44]. In a Korean population study, *HLA-A*2601* and two other alleles (*HLA-A*0207* and *HLA-A*3004*) were significantly associated with an increased risk of developing BD, and *HLA-A*2601* was associated with uveitis; *HLA-A*0207* was associated with skin lesions and arthritis; and *HLA-A*3004* was associated with vascular lesions, genital ulcers, and a positive pathergy test, suggesting that certain *HLA-A* alleles are responsible for the unique clinical features of BD [42]. *HLA-A*26* was not associated with BD in Palestine, Jordan, Iran, Ireland, Italy, or Turkey [45–49], although Remmers et al. [50] have reported a strong association between the *HLA-A* region and BD independent of *HLA-B*51* in a Turkish population.

There are at least four possible reasons why this association has not been observed in all populations. The first reason is that the frequency of the *HLA-A*26* allele differs among ethnicities. It is more common in Japan, Taiwan, and Korea than in other areas; therefore, the association between *HLA-A*26* and BD may have been easily observed in these countries. Actually, Hughes et al. [11] reported the low allele frequency of *HLA-A*26* in Turkish and Italian populations, in which the association with BD cannot be assessed, while a strong association was observed for *HLA-A*0201*. Second, there have been differences between studies regarding sample size and research strategy. Previous studies with negative results in *HLA-A*26* did not recruit enough samples to provide statistically significant results; they also did not stratify the study population according to *HLA-B*51* status. Third, the environmental factor(s) required for the development of BD associated with the *HLA-A*26* antigen are distributed unevenly throughout the planet. Finally, other genetic factors are highly important in the development of BD in populations in which no association has been observed between *HLA-A*26* and BD. Thus, the association between BD and *HLA-A*26* has not clearly been verified, and further studies are needed to assess the association of BD with *HLA-A*26*.

4.4.2 IL10 and IL23R-IL12RB2

In 2010, two GWASs by Remmers et al. [50] and Mizuki et al. [51] that employed a dense panel of single-nucleotide polymorphism (SNP) markers reported the genes that encoded IL-10 (*IL10*), IL-23 receptor (*IL23R*), and IL-12 receptor beta (*IL12B2*) as novel BD susceptibility loci, and demonstrated that polymorphisms in these loci are associated with the risk of BD in Turkish, Japanese, and Korean populations. The association of BD with *IL10* polymorphisms has also been reported in Iranian, UK, Jordanian, and Palestinian populations [52, 53], while the association of BD with *IL23R* polymorphisms has also been observed in Chinese populations [54]. In addition, in an Iranian population, *IL23R* and *IL12RB2* polymorphisms were significantly associated with BD and the importance of *IL23R* regulatory regions has been highlighted with respect to susceptibility to BD [53]. Therefore, it is highly possible that an immune response involving *IL10* and *IL23R* (or *IL12RB2*) contributes to BD development.

As *IL10* polymorphisms are associated with decreased *IL10* mRNA expression, it has been suggested that decreased expression of IL-10, which down-regulates Th1-type immune responses [55, 56], is related to the development of BD. *IL12RB2*, which encodes an IL-12 receptor chain, is expressed on Th1 and natural killer cells [57, 58]. *IL12RB2* polymorphisms might enhance responsiveness against IL-12, leading to excessive Th1 immune responses. Thus, the activation of a Th1 immune response derived from *IL10* and *IL12RB2* polymorphisms might be involved in BD development.

IL23R encodes a subunit of the IL-23 receptor. *IL23R* is expressed on Th17 cells and macrophages. Recent studies have suggested that Th17 cells are closely correlated with clearance of extracellular bacterial infection, neutrophil chemotaxis, and autoimmune disease development [59–61]. In BD patients, immune response and protection against certain streptococcal infections (e.g., *Streptococcus sanguinis* are enhanced) suggest that these bacterial infections may serve as triggers for the disease development [62]. As a result, excessive migration of neutrophils into the disease lesions might be induced by enhanced neutrophil functions, contributing to the pathogenesis of BD. *IL23R* polymorphisms might enhance responsiveness to IL-23 in Th17 cells and other IL23R positive cells, and accordingly, the Th17 cell-mediated adaptive immune response as well as an innate response might be activated and promote BD development.

4.4.3 STAT4

Two SNP GWASs (by Hou et al. in 2012 [63] and Kirino et al. in 2013 [64]) identified the *STAT4* (signal transducer and activator of transcription 4) gene as a susceptibility gene for BD and demonstrated that *STAT4* polymorphisms are associated with the risk of BD in Turkish, Japanese, and Chinese populations. A study in a Korean population has also reported the association of intestinal BD

with a *STAT4* polymorphism [65]. In addition, the study also reported that polymorphisms in *IL17A* and *IL23R* were associated with intestinal BD and that gene–gene interactions were observed between *IL17A*, *IL23R*, and *STAT4* polymorphisms, suggesting that the joint effect of SNPs in *IL17A*, *IL23R*, and *STAT4* genes may modulate susceptibility to intestinal BD.

STAT4 encodes a transcription factor that transmits signals induced by several key cytokines, including IL-12 and IL-23 [66]. STAT4 is an essential element in the early events of Th1 differentiation [67]. STAT4 has also been implicated in the production of IL-17 by the IL-23-differentiated cells, suggesting that it may be involved in the survival or maintenance of Th17 cells [68]. *STAT4* mRNA expression is reportedly higher in individuals with the BD-associated alleles (A alleles of rs7574070 and rs7572482) than in individuals lacking these alleles in a European population [64]. Since both IL-12 and IL-23 act through STAT4, the BD-associated *STAT4* alleles may induce upregulated IL-12 and IL-23 activity, which can lead to the development of BD. In a Chinese population, a BD-associated *STAT4* allele (the A allele of rs897200) was also associated with the upregulation of *STAT4* and the transcription and protein expression of IL-17 (a Th17 cytokine), but not interferon-γ (a Th1 cytokine) [63]. These findings suggest that the A allele of rs897200 in *STAT4* might contribute to the pathogenesis of BD through the Th17 pathway, but not the Th1 pathway.

4.4.4 ERAP1

The endoplasmic reticulum aminopeptidase 1 (ERAP1) is centrally involved in peptide trimming before HLA class I presentation. Previous GWASs have shown that *ERAP1* polymorphisms are associated with psoriasis and ankylosing spondylitis [69–71]. There is evidence for gene–gene interactions between *ERAP1* polymorphisms and the disease-associated HLA alleles in both diseases [70, 72]: *ERAP1* polymorphisms affected psoriasis and ankylosing spondylitis susceptibility only in individuals carrying *HLA-C*06* and *HLA-B*27*, respectively.

The SNP GWAS by Kirino et al. in 2013 [64] revealed that *ERAP1* polymorphisms are associated with BD in Turkish populations. The study also identified evidence of an interaction between *HLA-B*51* and *ERAP1*; *ERAP1* variants affected the risk for BD only in *HLA-B*51*-positive individuals, and homozygosity for the risk allele T at the *ERAP1* locus rs17482078 was associated with an odds ratio (OR) for BD of 3.78 among *HLA-B*51*-positive individuals and an OR of 1.48 among *HLA-B*51*-negative individuals. These findings indicate that the BD-associated *ERAP1* variant contributes to disease susceptibility through an interaction with the *HLA-B*51* protein and that modulation of *ERAP1* may be effective in treating BD, especially in *HLA-B*51*-positive patients.

4.4.5 CCR1-CCR3

The SNP GWAS by Kirino et al. in 2013 [64] also identified BD-associated polymorphisms in the *CCR1* (chemokine (C–C motif) receptor 1)-*CCR3* region in Turkish and Japanese populations. Strong association signals were located in the 3′ untranslated region (UTR) of *CCR1*. The strongest, rs7616215, is located within DNase I hypersensitivity and histone 3 lysine 4 methylation sites, suggesting that the polymorphisms have an effect on transcription. The study actually demonstrated a significant correlation between the disease risk T allele of rs7616215 and enhanced expression of *CCR1* mRNA, but not *CCR3* mRNA. In addition, the study also found that the migration of monocytes in response to a gradient of the CCR1 ligand MIP1-α was less pronounced in T allele-positive individuals than in T allele-negative individuals, and that *CCR1* mRNA expression correlated significantly with the chemotactic activity of monocytes against a gradient of MIP1-α. Therefore, the study results suggest that impaired clearance of pathogens may contribute to the etiology of BD. Hou et al. reported that the *CCR1-CCR3* polymorphisms were also associated with BD in a Chinese population: rs13084057 in the 3′ UTR of *CCR1*, and rs13075270 and rs13092160 in the intergenic region between *CCR1* and *CCR3* (the 5′ UTR of *CCR1* or the 5′ UTR of *CCR3*) [73]. The study demonstrated that *CCR1* and *CCR3* mRNA expression were reduced in individuals with the TT genotype of rs13092160 (homozygosity for the risk allele), compared with those carrying the CT genotype (heterozygosity for the risk allele), suggesting that both *CCR1* and *CCR3* genes may contribute to the development of BD.

CCR1 and *CCR3* encode the beta chemokine receptor family, which belongs to the G protein-coupled receptor super family. These receptors play an important role in the recruitment and activation of inflammatory cells and contribute to autoimmune and allergic diseases [74, 75]. They are closely located in chromosome 3p21.3 and are considered to have originated from a common ancestral gene, suggesting that the expression of these genes may be regulated through similar pathways [76, 77]. Further investigation is needed to clarify the significance of *CCR1* and *CCR3* in the etiology of BD.

4.5 Conclusion

This chapter summarizes the genetic susceptibility factors for BD identified to date. In addition to the genes discussed above, the *KLRK1* (killer cell lectin-like receptor subfamily K, member 1)-*KLRC4* (killer cell lectin-like receptor subfamily C, member 4) locus on chromosome 12p13.2-p12.3 [64] and the *GIMAP* (GTPases of immunity-associated protein) locus on chromosome 7q36.1 [78] have been identified by GWASs and might also be important for the development of BD. Recent GWAS findings provide new insights into the genetic tendency underlying BD by connecting classically known findings and allow for clearer interpretation

of the etiology and pathophysiology of BD at the molecular level. Thus, findings from genetic studies can provide useful clinical information and open the door to the development of more accurate and reliable diagnostic and treatment approaches for BD.

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Infections, Autoimmunity, and Behçet's Syndrome: What Liaison?

5

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5.1 Immune Responses to Infections

During the course of evolution, the immune system had to continuously shape and refine its mechanisms of defense against pathogens. In response to different microorganisms, specialized types of specific responses allow the recognition and elimination of infectious agents. Viruses, which grow within the infected cell, can be successfully eliminated only by killing their host cells by CD8 class I major histocompatibility complex (MHC)-restricted cytotoxic T lymphocytes, which recognize viral antigens synthesized within infected cells and present on their surface in the context of class I MHC molecules. In contrast, most microbial antigens are endocytosed by antigen-presenting cells (APC), processed and presented preferentially in association with MHC class II molecules to $CD4^+$ class II MHC-restricted Th cells. $CD4^+$ T cells aid B cells in the production of antibodies, which challenge

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extracellular microorganisms or neutralize their exotoxins (humoral immunity). Some microorganisms such as mycobacteria, however, can survive within macrophages in spite of the microbicidal activity of these cells unless CD4 Th cells reactive to mycobacterial antigens activate macrophage production of reactive oxygen intermediates, nitric oxide, and tumor necrosis factor (TNF)-α, leading to the microorganism's destruction (cell-mediated immunity). Most immune responses against pathogens involve both arms of the immune system (humoral and cell-mediated immunity) acting in concert [1].

During the effector-specific immune response, different patterns of cytokine profiles are characteristic of certain Th-cell subsets, whose polarized forms are Th1, Th2, and Th17 cells [1]. Th1 cells producing IFN-γ and TNF-β elicit macrophage activation and B cell production of opsonizing and complement-fixing antibodies, whereas Th2 cells producing IL-4, IL-5, IL-10, and IL-13 induce the production of high levels of antibodies, including IgE, and eosinophils. The types of effector responses are tightly regulated and usually mutually exclusive. A new subset of Th cells, named Th17 cells, producing IL-17 alone or in combination with IFN-γ, has been identified recently [2]. Th17 cells play a critical role in protection against microbial challenges, particularly extracellular bacteria and fungi [3].

The factors responsible for the Th cell polarization into a predominant Th profile have been extensively investigated. Current evidence suggests that Th1, Th2, and Th17 cells develop from the same Th-cell precursor under the influence of mechanisms associated with antigen presentation [4, 5]. Both environmental and genetic factors influence the Th1 or Th2 differentiation mainly by determining the "leader cytokine" in the microenvironment of the responding Th cell. IL-4 is the most powerful stimulus for Th2 differentiation, whereas IL-12, IL-18, and IFN-γ favor Th1 development [6–8]. A role has been demonstrated for the site of antigen presentation, the physical form of the immunogen, the type of adjuvant, and the dose of antigen [9]. Several microbial products (particularly from intracellular bacteria) induce Th1-dominated responses because they stimulate IL-12 production. IFN-α and IFN-γ favor Th1 development by enhancing IL-12 secretion by macrophages and maintaining the expression of functional IL-12 receptors on Th cells [10]. On the other hand, IL-11 and PGE2 promote Th2 cell polarization [11, 12]. Th17 cells represent a distinct subset of effector T cells induced as a consequence of IL-23 production by DCs [13]. IL-23 is a heterodimer that shares the p40 chain with IL-12, but differs in the presence of a p19 instead of the p35 chain. Similar subunit sharing occurs for the IL-12R and the IL-23R: the IL-12R is a heterodimer composed of β1 and β2 chains, whereas the IL-23R contains the β1 chain but in combination with a specific receptor known as IL-23R [14]. Both in vitro differentiation of Th17 cells and in vivo Th17-mediated inflammation are dependent on the transcription factor retinoic acid receptor-related orphan receptor γ-t (RORγt) [15]. Some microbial products and stimuli induce a preferential activation of Th17 responses [16, 17]. Moreover, regulatory T cells (Treg) are a subset of T cells that are physiologically devoted to the maintenance of self tolerance and to the regulation of Th responses. Treg play a crucial role in regulating the effector immune responses in the different districts of the organism by

suppressing the activation and proliferation of antigen-specific T cells, and an abnormal Treg activation might lead to impaired tumor immunity. Treg are able to suppress T-cell responses, via both cell contact and by soluble factors, such as TGF (transforming growth factor)-β and IL-10 [18].

In most human infections, specific immunity is of crucial importance, but an inappropriate response may not only result in lack of protection, but even contribute to the induction of immunopathology. In human leishmaniasis, lack of IFN-γ and high IL-4 production predict progression into fulminant visceral disease, whereas individuals whose cells produce large amounts of IFN-γ usually remain asymptomatic [19]. Th1 cytokine mRNA signals were found in the skin of patients with localized and mucocutaneous leishmaniasis, whereas Th2 cytokine mRNA were highly expressed in the skin of patients with destructive forms of cutaneous or active visceral disease [20]. Interestingly, IFN-γ in combination with pentavalent antimony was effective in treating severe or refractory visceral leishmaniasis [21].

Parasitic infections, characterized by eosinophilia and elevated IgE levels, usually elicit Th2 cytokines. Th2 responses, which down-regulate host protective Th1 functions, are less detrimental to parasites; on the other hand, the host would avoid immuno-pathological reactions related to strong, but harmful, Th1 responses. The pathology resulting from *Schistosoma mansoni* infection is indeed predominantly caused by the host Th2 response leading to chronic granulomatous reaction and consequent damage to the intestine and liver [22, 23].

In the immune response to bacterial infections, Th2 cells seem to be appropriate opponents against toxin-producing bacteria, since Th2 cytokines favor B-cell maturation and production of neutralizing antibodies. In contrast, intracellular bacteria (e.g., *Listeria monocytogenes*, *Mycobacteria*, *Salmonellae*) are appropriately encountered Th1 cells, which produce cytokines able to activate macrophages and cytotoxic T cells. Mice with disrupted IFN-γ or IFN-γ receptor genes and producing high levels of IL-4 succumb to mycobacterial infections [24], whereas mice resistant to *M. bovis* produce high levels of IFN-γ and low amounts of IL-4 [25]. Likewise, patients with IFN-γR or IL-12R deficiency are extremely sensitive to mycobacterial infections and develop severe and often fatal disease [26, 27].

The predominance of one or the other Th response in any infectious disease is probably modulated by both the pathogen and the genetic background of the host, whose innate immunity plays a key role. Since bacteria possess several components which can trigger IL-12 production by macrophages, it is not surprising that most of them favor Th1 development. These "Th1 inducers" include the lipoarabinomannan of mycobacteria, teichoic acids of Gram-positive bacteria and lipopolisaccharides of Gram-negative bacteria or viral polynucleotides [28]. In genetically predisposed individuals, some strong and persistent Th1 responses against bacteria may often result in immunopathological reactions, such as reactive arthritis following infection with *Yersinia entero-colitica* [29].

In *Aspergillus fumigatus* and *Candida albicans* infection, a strong Th17 response has been documented and related to either protection or immunopathology [5, 30]. It has been recently demonstrated that the adenylate cyclase toxin of *Bacillus anthracis* is a potent promoter of Th17 cell development [17]. The toxin selectively targets specific signalling modules in the T-cell receptor (TCR) signaling cascade through its cyclic AMP (cAMP)-increasing activity, thereby promoting Th17 cell development. Further, some of the autoimmune responses formerly attributed only to Th1 cells, such as experimental autoimmune encephalomyelitis, collagen-induced arthritis, some forms of inflammatory bowel disease, have now been shown to be mediated, at least in part, by Th17 cells [1].

5.2 Infections and Autoimmunity

All individuals harbor autoreactive T cells that need activation and critical expansion in order to start active autoimmune disease [31]. In a number of human diseases and in their corresponding experimental animal models, it has been suggested that pathogens can induce disease through autoimmune mechanisms [32–36].

Several mechanisms have been proposed for how pathogens might induce activation and critical expansion of autoreactive T cells and start autoimmune disease. Viral and bacterial superantigens, that bind a variety of MHC class II molecules and activate large proportions of T cells, irrespective of their specificity, can also lead to activation of resting autoreactive T cells [37].

Tissue inflammation induced by pathogens may result in local activation of antigen-presenting cells (APC) and in enhanced processing/presentation of self antigens that cause T-cell priming. T-cell activation would then be followed by expansion of T cells with additional specificities, a phenomenon referred to as epitope spreading [38, 39]. Another mechanism by which pathogens can start autoimmune disease would imply that the inflammatory setting and the paracrine secretion of T-cell growth factors induce the expansion of activated autoreactive T cells, whose small number was previously insufficient to set up the disease. Such a mechanism is referred to as bystander activation [40]. Moreover, a microbial antigen can include an epitope that is structurally similar to an autoantigen epitope, providing the basic element of the mechanism referred to as molecular mimicry [38, 41–44].

5.3 Borrelia and Lyme Arthritis

A clear example of epitope mimicry in humans is Lyme arthritis (LA), in which *Borrelia burgdorferi* disseminates to multiple tissues, including joints. In the synovial of patients with specific MHC class II haplotypes, activation of Th1 cells reactive to the 165–173 peptide of the outer surface protein A (OspA) of

B. burgdorferi occurs [45, 46]. Such an OspA epitope is similar to the L332–340 peptide of the human leukocyte function-associated antigen 1α (LFA-1α), whose expression is up-regulated on synoviocytes by the Th1-derived IFN-γ [47, 48]. Recent studies, however, have shown that LA can be induced by cytokines other than IFN-γ because experimental LA can occur and propagate even in IFN-γ deficient mice. We have recently demonstrated that T cells from synovial fluid of patients with LA produce IL-17 in response to NapA, a major antigen produced by *B. burgdorferi* [49]. Indeed, inhibition of IL-17 prevents the development of arthritis in vaccinated mice challenged with *B. burgdorferi*. Furthermore, NapA is able to stimulate monocyte expression of IL-23, IL-6, TGF-β, and IL-1-β, key cytokines for Th17 cell differentiation. Since Th1 an Th17 cells dominate the immune response in the synovial fluid of patient with LA, it has been suggested the possibility that such T cells are indeed effectors of an autoimmune process [46, 48–50]. In accordance with the fact that both Th1 and Th17 cells are involved in LA pathogenesis, there is a prominence of some chemokines crucial for their recruitment into the synovial fluids of patients, such as CXCL10, specific for Th1 cells, and CCL2, specific for both Th1 and Th17 cells [51, 52]. Thus, on the basis of the results obtained so far, it can be hypothesized that the protein NapA, which accumulates in the joint cavity of LA patients, recruits PMNs in the early stage of the disease and, subsequently, T lymphocytes. NapA acts with the contribution of chemokines (such as CCL2, CCL20 and CXCL10) released by PMNs in recruiting T cells. The latter are not only Th1 or Th17 cells, but include also a subset producing both IFN-γ and IL-17. Together, our results highlight NapA as a major bacterial factor in driving the generation of a pro-inflammatory T-cell response responsible for clinical onset and histopathological changes in LA.

5.4 *Helicobacter pylori* and Gastric Autoimmunity

Another example of molecular mimicry is gastric autoimmunity in the course of *Helicobacter pylori* infection. *H. pylori* is a Gram-negative pathogen that causes persistent infection in half the world population. *H. pylori* infection results in a series of various clinical outcomes, including transient and almost asymptomatic gastric inflammation, chronic gastritis, peptic ulcer disease, mucosal atrophy, gastric carcinoma, or gastric B-cell lymphoma of the mucosa-associated lymphoid tissue (MALT) cells [53]. Loss of gastric glands in the *antrum* and *corpus*, which is referred to as atrophy, is considered a precursor of gastric adenocarcinoma, the second most frequent cause of cancer-related death, and there is strong evidence that *H. pylori* infection increases the risk of gastric cancer cells [53, 54]. The trigger of atrophy and the mechanism involved in its development are still unknown. Although *H. pylori* is not invasive and usually resides in the antrum, glands located deep in the mucosa of antrum and corpus disappear. Accumulating data in humans suggest the gastric corpus atrophy is caused by an autoimmune process associated with *H. pylori* infection.

A strong association between *H. pylori* infection and gastric autoimmunity has been highlighted by a number of clinical and epidemiological studies indicating that most of patients with AIG have or have had *H. pylori* infection [55]. *H. pylori*-associated autoimmune gastritis (AIG) is characterized by an inflammatory infiltrate of the gastric mucosa, including T cells, macrophages, and B cells. It mainly affects the corpus and the *fundus*, and it is accompanied by loss of gastric parietal and zymogenic cells. We have characterized at molecular level the gastric T-cell mediated responses to *H. pylori* and to the H^+, K^+-ATPase autoantigen in a series of *H. pylori*-infected patients with gastric autoimmunity [55].

Among gastric Th clones, a number proliferated to *H. pylori*, but not to the *H. pylori* proteins CagA, VacA, hsp, urease nor to H^+, K^+-ATPase. Some other Th clones proliferated to H^+, K^+-ATPase and not to *H. pylori* (autoreactive), and a third group of clones was found that proliferated to both *H. pylori* and H^+, K^+-ATPase (cross-reactive) [56]. All the Th clones able to proliferate to H^+, K^+-ATPase were studied for their ability to respond to the 261 overlapping 15-mer peptides covering the amino acid sequence of α and β chain of the human H^+, K^+-ATPase. The majority of cross-reactive Th clones recognized their epitope in the chain whereas only a few clones in the β chain. On the other hand, most autoreactive Th clones recognized their epitope in the β chain, some in the β chain of the proton pump. Therefore, some "shared" H^+, K^+-ATPase epitopes, mainly in the α-chain, are cross-reactive with epitopes of *H. pylori* antigens, whereas others can be considered as "private" epitopes of H^+, K^+-ATPase. A cross-reactive *H. pylori* peptide could be found for each of the H^+, K^+-ATPase/*H. pylori* cross-reactive gastric Th clones. Overall, that study led to the identification of nine different *H. pylori* proteins (such as lipopolysaccharide biosynthesis protein, histidine kinase, porphobilinogen deaminase, dimethyl-adenosine transferase, glucose-inhibited division protein A, VirB4 homolog, phosphoglucosamine mutase, acetate kinase, and penicillin-binding protein-2) each harboring a T-cell peptide suitable for cross-reaction with T-cell epitopes of gastric H^+, K^+-ATPase α-chain [55]. Interestingly, none of the bacterial epitopes recognized by cross-reactive Th clones belong to the well-known *H. pylori* immunodominant antigens, such as CagA, VacA, and urease, which are major targets of gastric T-cell responses in *H. pylori* infected patients with peptic ulcer [57]. Two possibilities can be considered: these peptides are implicated in cross-reactivity because of their structural properties or alternatively a physiological relevance implicating these particular nine proteins can be postulated. All the cross-reactive and autoreactive H^+, K^+-ATPase-specific Th clones after activation were able to induce cell death via either Fas–Fas ligand-mediated apoptosis or perforin-mediated cytotoxicity against target cells [55]. This ability to induce apoptosis in T cells might give a selective advantage that can promote survival and persistence of bacteria, allowing *H. pylori* to escape the host immune response. On the other hand, the relevance of cross-reactive and autoreactive cytolytic Th effector cells in the genesis of AIG is consistent with data in the mouse model that Fas-related death is required for the development of full-blown destructive autoimmune gastritis [58]. Based on these results, it is tempting to speculate that in the "gastric autoimmune

inflammatory *scenario*" in which cross-reactive and autoreactive Th clones are activated, parietal cells might become target of the pro-apoptotic and cytotoxic activity of cross-reactive and autoreactive gastric Th cells. The end point of this process would be gastric corpus atrophy and hypochlorydria.

5.5 *Chlamydophila pneumoniae* and Atherosclerosis

Chlamydophila pneumoniae is an obligate intracellular bacterium present as free infectious, nonmetabolic elementary bodies (EB) that transmit infection to susceptible eukaryotic cells such as epithelial and endothelial cells, smooth muscle cells, and macrophages. During its developmental cycle, *C. pneumoniae* differentiates into metabolically active reticular bodies (RB) able to replicate by binary fission and differentiate into EB, which cause host cell lysis, thereby progressing the infectious cycle [59]. Productive infection is not the only possible outcome of *C. pneumoniae* interaction with host cells. Persistence due to nutritional deprivation, antibiotic treatment, or immune reaction leads to a chronic or latent infection characterized by the presence of abnormal RB that fail to mature [60]. Some aspects of the developmental cycle of *C. pneumoniae* suggest a direct implication of phospholypase D (PLD) in pathogenesis, specifically by affecting the regulation of lipid metabolism and lipid exchange between *C. pneumoniae* and host cells. Over the past two decades, a strong link between inflammation and atherosclerosis has been highlighted [61]. A pathogenetic role in atherosclerosis has also been suggested for chronic bacterial infections, such as *H. pylori* or *C. pneumoniae*, leaving still open the question of how the infectious agents might contribute to the formation of plaques [62]. We in-depth investigated the functional profile of in vivo activated T lymphocytes that infiltrate atherosclerotic plaques [16, 63, 64]. Among patients undergoing carotid endarterectomy, we selected 30 *H. pylori*-infected individuals, fifteen of whom were also seropositive for anti-*C. pneumoniae* antibodies (Cp-pos), and fifteen were seronegative (Cp-neg). Fragments of carotid plaques of all patients were cultured in IL-2-conditioned medium to allow the preferential expansion of in vivo activated T cells resident in the plaques. Single T-cell blasts were then cloned and studied. In all patients, the majority of plaque-derived Th clones produced IFN-γ and TNF-α, but not IL-4, and were able to provide help for tissue factor (TF) production by autologous monocytes. Some clones were able to produce IL-17 alone or in combination with IFN-γ. We studied the proliferative response to *H. pylori* and *C. pneumoniae* antigens of plaque-derived Th clones. We could not find any T-cell reactivity against *H. pylori* antigens in the atherosclerotic patients [63]. In contrast, 25 % of the Th cell clones generated from the fifteen Cp-pos patients were specific for *C. pneumoniae* antigens, such as OMP-2, hsp 60, and hsp 10. The majority of clones able to produce Th17 cytokines were specific for Cp-PLD (pnas 12). CpPLD-specific T cells were able to strongly promote the production of TF and metalloproteinase 9 (MMP-9) involved in plaque rupture and atherothrombotic

events. CpPLD was also able to activate monocytes by binding Toll-like receptor 4 (TLR4), leading to the production of IL-23, IL-6, IL-1β, TGF-β, and CCL-20, molecules critical for the generation, differentiation, and maintenance of Th17 cells. Furthermore, CpPLD was able to elicit the up-regulation of the expression of several chemokines and adhesion molecules such as CXCL-9, CCL-20, CCL-4, CCL-2, ICAM-1, and VCAM-1 in human venular endothelial cells (HUVECs) [16].

Epidemiological, clinical, and experimental studies in animal models not only suggest the potential importance of inflammation in atherosclerosis but also support the hypothesis that immune responses to antigens (Ags) of pathogens cross-react with homologous host proteins due to molecular mimicry [61, 63]. Protein candidates involved may be the stress-induced proteins known as heat shock proteins. We recently reported that atherosclerotic plaques harbor in vivo-activated Th cells that recognize the human 60 kDa hsp. Such in vivo-activated 60 kDa HSP-specific T cells are not detectable in the peripheral blood. Most of plaque-derived T cells specific for human 60 kDa hsp also recognized the *C. pneumoniae* 60 kDa hsp. We characterized the submolecular specificity of such 60 kDa hsp-specific plaque-derived T cells and identified both the self and cross-reactive epitopes of that autoantigen [64]. The cross-reactive human peptide of hsp displayed high sequence homology to the corresponding Cp peptide whereas the autoreactive peptide showed very low, if any, homology with the Cp peptide challenge with human 60 kDa hsp, most of the plaque-derived T cells expressed Th type 1 functions, including cytotoxicity and help for monocyte TF production. We suggest that arterial endothelial cells, undergoing classical atherosclerosis risk factors and conditioned by Th type 1 cytokines, express self 60 kDa HSP, which becomes target for both autoreactive T cells and cross-reactive T cells to microbial 60 kDa hsp via a mechanism of molecular mimicry. This hypothesis is in agreement with the notion that immunization with hsp exacerbates atherosclerosis, whereas immunosuppression and T-cell depletion prevent the formation of arteriosclerotic lesions in experimental animals [65–67]. Thus the results obtained so far demonstrated that atherosclerosis can result from inappropriate Th1 and Th17-driven immunopathological responses, part of which due to *C. pneumoniae* and molecular mimicry, and suggest that Th1 and Th17-cells play a crucial role in plaque rupture and atherothrombotic events.

5.6 Behçet's Syndrome and Infections

As in AIG, LA and atherosclerosis, the possibility exists that infections might play a role in the genesis of Behçet's syndrome (BS).

As in atherosclerosis [64], it has been hypothesized that immunopathological responses can be evoked in BS by different microbial products, such as heat shock proteins. Hsp may induce damage via several mechanisms. Giving the high homology between the bacterial 65 kDa hsp and the human 65 kDa hsp [68]

recurrent infections by hsp-containing bacteria may induce, via molecular mimicry, the activation of autoimmunity through pathogenic hsp-specific T cells in genetically predisposed subjects. Hsp-specific T cells are indeed well-known for their ability to mediate tissue damage by both production of Th1 cytokines, such as IFN-γ and TNF-α and activation of cell-mediated cytotoxicity [55, 64].

Actually it has been shown that in patients with BS antibodies directed to several hsp 65 epitopes are present. IgA antibodies specific for mycobacterial hsp 65 are signficantly increased in patients with BS [69, 70]. Antibodies specific for 65 kDa antigens of both *S. sanguinis* and *S. pyogenes* (similar to mycobacterial hsp 65) and oral mucosal extracts, were detected in BS. Moreover IgG and IgA antibodies directed to different hsp peptides (such as human 336–351, 136–150, and mycobacterial 311–325, 154–172, 111–125) are significantly increased in patients with BS [71]. Some of the human and mycobacterial hsp peptides, e.g., 111–125, 154–172, 219–233, 311–325, have been shown to induce T-cell activation in patients with BS. When administered to rats, both mycobacterial and human homologous peptides were able to induce uveitis, and to develop specific antibody response against hsp peptides [72, 73]. It is of note that hsp 60 may act, directly or indirectly, via T cells, by stimulating the expression of vascular endothelial growth factor (VEGF), which may induce both vasculitis and thrombosis, by damaging endothelial cells [74].

Other cells of the immune system and cytokine networks leading to the production of IL-6 and IL-1, have been shown to be involved in the course of BS.

$\gamma\delta$ T cells, which are very important in the mucosal oral defense of the host, have been shown to be, at least in part, related to the immunopathology of BS and are increased in the peripheral blood of patients with BS, especially in the active phase of the disease [75, 76] and produce high levels of inflammatory cytokines such s IFN-γ and TNF-α [75, 77] following stimulation with hsp and other microbial antigens [76, 78].

Thus, on the basis of the results obtained so far, we can hypothesized that even in BS, although not yet proven, the damage might be the final result of different and complex immunopathological pathways, at least in part related to peculiar infections (yet to be identified) and to the consequent activation of immune response.

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Pathogenesis of Behçet Syndrome

6

Giacomo Emmi, Danilo Squatrito, Elena Silvestri, Alessia Grassi and Lorenzo Emmi

6.1 Main Actors and Battlefield

6.1.1 Genetic Background

The present review will not address specifically the genetic background of BS, since it has been already described in Chap. 4. HLA class I B*51 allele has been strongly associated with BS in many different ethnic groups, even if it cannot be found in all patients [1, 2]. However, a genetic predisposition is probably more complex and based on HLA and non-HLA allele polymorphisms (see Fig. 6.1).

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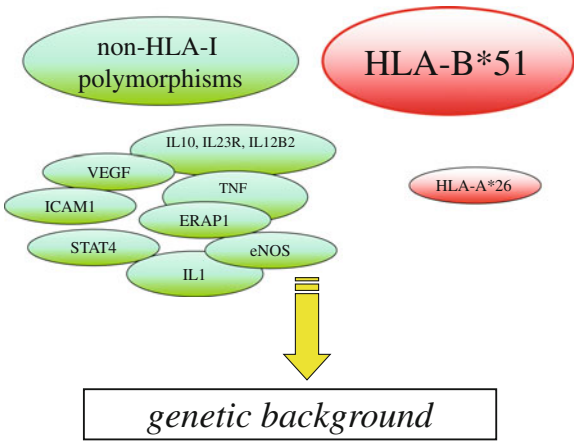

Fig. 6.1 HLA and non-HLA allele polymorphisms in Behçet syndrome

6.1.2 Infectious Agents

A putative role for environmental factors in BS, especially bacterial and viral agents, has been postulated during the last few years (see also Chap. 6).

Bacteria. A probable role of oral flora has been considered in the etiopathogenesis of BS given the high frequency of oral ulcers [3], particularly after dental interventions [4]. The most investigated microorganism is *Streptococcus sanguinis* and the main data supporting his role as a pathogenic trigger in BS are the following:

- *Streptococcus sanguinis* has been detected more frequently in the oral flora of BS patients compared to healthy controls [5–8].
- both Streptococcus sanguinis and sera of patients with BS are able to stimulate endothelial cells [9].
- serum antibody titres against *Streptococci* are often elevated and specific antibodies to 65 kDa antigens of Streptococcus have been detected from BS patients sera [10–11].
- BS patients have in oral cavity uncommon Streptococcus sanguinis serotype, such as KTH-1, significantly more frequently than healthy controls [12, 13].
- *Streptococcus*-related BES-1 gene-derived peptides, homologous to heat shock protein (Hsp)-60 and retinal proteins, have been found to be able to stimulate peripheral blood mononuclear cells (PBMC) of BS patients [14].
- BS patients show skin test hypersensitivity with different streptococcal antigens [15] and recently a positive pathergy test has been proved to be more sensitive with bacteria rich self-saliva as compared to sterile saliva (this more evident pathergy reaction is considered to be caused by oral *Streptococci*) [16].

Many other bacterial species such as *Helicobacter pylori* [17], *Mycobacteria*, or *Borrelia burgdorferi* [18] were occasionally reported as putative BS triggers but without strong level of evidence.

Viruses. So far many viruses have been investigated for a possible role in the etiopathogenesis of BS, including Herpes Simplex Virus (HSV), Cytomegalovirus, Varicella Zoster Virus, and Epstein-Barr Virus [19–27], but the more convincing data have been reported for HSV:

- HSV-1 DNA has been detected in PBMC and in oral and genital ulcers from BS patients;
- higher titres of serum antibodies against HSV-1 are reported in sera of BS patients;
- in experimental mice models inoculation of HSV has been able to cause lesions resembling human BS.

6.1.3 Immune System Dysregulation

6.1.3.1 Innate immunity

The innate immune system, also known as nonspecific immune system, comprises cells that represent the first line host defence against pathogens, with immunological mechanisms distinct from acquired or adaptive immunity. Classically, cells of the innate immune system recognize and respond to microorganisms using a generic or not-specific recognition system, but they do not confer long-lasting protective immunity to the host. The main actors of this first defence system are represented by macrophages, dendritic cells (DCs), and neutrophils. These cells present on their membrane surfaces receptors such as pattern recognition receptors (PRRs), which recognize molecules, distinct from the host ones, that are broadly shared by different pathogens. These highly conserved molecules are also collectively referred to as pathogen-associated molecular patterns (PAMPs) and when activated by them, the PRRs present on innate immune system cells, release inflammatory mediators responsible for the clinical signs of inflammation. Toll-like receptors (TLRs) work as sensors for PAMPs and are considered crucial for the initiation of innate immune responses. Exogenous TLR ligands include lipoteichoic acid, lipopolysaccharide (LPS), motifs of bacterial and viral DNA [28–31]. Recently, many studies have addressed the role of endogenous ligands in TLR-mediated cell activation [32–35]. Intriguingly, such endogenous ligands, including Hsp, are released upon tissue damage and cell stress, events that are likely to occur in inflammatory conditions. TLRs are implicated in the breakdown of tolerance, as shown in experimental models of celiac disease, diabetes and multiple sclerosis [36–39]. Hsp60/65 is a common ligand for TLR-2 and TLR-4 [36, 37] and TLR-2- as well as TLR-4-expressing cells are accumulated in the intestinal lesions of BS. IL-12 produced by TLR-2-expressing cells is considered a key cytokine that contributes to the induction of Th1-dominant immune responses in intestinal BS.

Dendritic cells. DCs are antigen presenting cells (APC) which play a pivotal role in the polarization of immune adaptive response; only few data are available about their possible role in the pathogenesis of BS. Quite recently, Pay et al. demonstrated a decrease percentage of peripheral plasmocytoid DCs (pDCs), probably due to their migration from circulation to target tissues during inflammation. Notably

IFN-α, mainly produced by pDCs, is increased in patients with BS, particularly when the disease is active [38]. Epidermal Langerhans cells are increased at the site of pathergy reaction [39]; furthermore, it has been shown that these cells are more active in BS patients as compared to controls [40, 41].

Natural killer cells. As major components of innate immunity, natural killer (NK) cells not only exert cell-mediated cytotoxicity against tumor or infected cells, but also regulate other immune cell functions by secretion of cytokines and chemokines. Due to these effector functions, NK cells play a significant role in host defense against malignancies and certain viruses, but they may also be important in the regulation of autoimmunity [42]. At the moment only conflicting data about their role in the pathogenesis of BS exist [43–45].

γδT cells. While most T cells use a classic CD3-associated αβT cell receptor as antigen recognition structure, a second population of T cells express the alternative γδT cell receptor. γδT cells are a minor population in the peripheral blood, but constitute a major population among intestinal intraepithelial lymphocytes. Most γδT cells recognize in a non-MHC-restricted manner ligands different from the short peptides that are seen by αβT cells in the context of MHC class I or class II molecules. Thus, human Vδ2 T cells recognize small bacterial phosphoantigens, alkylamines and synthetic aminobisphosphonates, whereas Vδ1 T cells recognize stress-inducible MHC-related molecules MICA/B as well as several other ligands. At the functional level, γδT cells rapidly produce a variety of cytokines and usually exert potent cytotoxic activity, also toward many tumor cells. γδT cells represent a bridge between innate and adaptive immune system, since their T cell receptors recognize conserved regions of microbic antigens and ultimately work as a PRR. In the *continuum* of immune protection and homeostasis γδT cells stay in the middle between innate NK cells and the adaptive αβT cells [46]. The role of these cells in the pathogenesis of BS is supported by the following considerations:

- BS has a predominant muco-cutaneous involvement and γδT represent the first defense line at mucosal level;
- peripheral blood γδT cells were reported to be increased in several BS studies [47, 48];
- γδT cells were detected in bronchoalveolar lavage and cerebral spinal fluid (CSF) of BS patients [49];
- γδT cells obtained from BS patients showed activation and high proliferative responses to different microbial products [50–56];
- γδT cells produce a higher amount of IFN-γ and TNF-α in active BS compared to inactive ones [47, 49, 52];
- Vγ9/Vδ2 T cells are activated in patients with active BS and express increased levels of TNF-α receptors and IL-12 receptors [50];
- granzyme A, both in serum and in Vγ9/Vδ2 T cells supernatants of active BS patients, is present [50];
- T cells responsive to Hsp 60 derived-peptide are mainly γδT cells, albeit this was reported only in UK patients [57].

Neutrophils. Polymorphonuclear (PMN) neutrophils which play an important role in innate immunity and in BS pathogenesis, can be activated both by APC and

T cells [58]. Their central role in BS pathogenesis is supported by the following data:

- neutrophils in BS present an increased chemotaxis, phagocytosis, superoxide generation and myeloperoxidase production [59];
- PMNs hyperactivation is confirmed by an increased expression of activation markers such as CD11a, CD10 and CD14 on cell surface [60];
- transgenic HLA-B*51 mice show enhanced neutrophil function [61];
- growth-related oncogene-a (GRO-α) is a potent chemoattractant for and activator of neutrophils and is significantly elevated in the serum of patients with active disease [62];
- neutrophils derived from BS patients present a significant increase of their lifespan [59].

Autoinflammation. The central role of innate immunity in BS pathogenesis is also suggested by the increased levels of IL-1 in this condition and by the good therapeutic response to IL-1 blocking agents recently reported, as occurs in autoinflammatory diseases. Autoinflammatory syndromes are genetic inherited entities that cause an uncontrolled release of the proinflammatory cytokines with consequent recurrent spontaneous inflammatory events and fever in the absence of antigen-specific T cell response or circulating autoantibodies. The list of autoinflammatory diseases has grown during the last decade, and some authors have recently suggested that, since BS shared some common features with them, may be classified into the group of autoinflammatory disorders [63, 64].

6.1.3.2 Adaptive immunity

The adaptive immune system, or acquired immune system, is composed by highly specialized cells and involves a tightly regulated interplay between APC and T and B lymphocytes, which facilitate pathogen-specific effector pathways, generation of immunologic memory, and regulation of host immune homeostasis.

Th1 lymphocytes. These cells have a pivotal role in orchestrating adaptive immunity and seem to have an important role in the pathogenesis of BS. The evidence for a critical role of these cells is supported by much evidence. In particular, an increase in Th1 cytokine (IFN-γ, IL-12, IL-18) and chemokines receptors (CCR5, CXCR3 and CCL-2) production has been demonstrated in [65–70]:

- peripheral blood of active BS patients
- culture supernatants of stimulated PBMC with polyclonal mitogen
- cytoplasm of mononuclear cells at mRNA level
- ileal, mucocutaneous and skin lesions of active BS patients.

Th1 cells infiltrates were also reported in genital ulcers, pseudofolliculitis, gastrointestinal and pathergy test lesions of BS patients [69, 71, 72].

Th17 lymphocytes. Th17 cells, a distinct CD4+T lineage from Th1 or Th2 with a specific-related transcription factor, producing different cytokines (IL-17A/F, IL-21, IL-22, IL-26) and chemokines (CXCL8), are active on both nonimmune and immune cells. High levels of IL-17 and IL-23 have been reported in PBMC from active BS patients; furthermore, IL-17+ cells were found to infiltrate the erythema

nodosum-like lesions of these patients [73]. The expression of specific Th1 and Th17 transcription factors was also determined in BS patients; in particular, expression of TBX21 (Th1), RORC (Th17), and FOXP3 (Treg) transcription factors were increased in neuro-Behçet patients (NB) compared to healthy controls, while Th2-associated GATA3 expression were found to be significantly decreased. Interestingly, an increase in the RORC/FOXP3 and TBX21/GATA3 ratios was found in these patients indicating that both Th1 and Th17 mRNA expression can determine Treg cells impairment [74]. Moreover, Pineton et al. [75] demonstrated an increase of Th17 cells and decrease of Tregs in peripheral blood of BS patients, and Th17 increase seems to correlate with disease activity. CD4+ T cells producing IL-21 were found to be remarkably increased in peripheral blood of BS patients and positively correlate with Th17 and negatively with Tregs. IL-17 and IL-21 producing cells were demonstrated in CSF, brain inflammatory infiltrates and intracerebral blood vessel of NB patients; furthermore, IL-21 blockade using an IL-21R-Fc construct restored Th17 and Treg homeostasis in BS [76]. Interestingly, IFN-α has been shown to up-regulate IL-10 and, consequently, to inhibit IL-17 production in PBMC of BS patients [77].

T regulatory cells. Conflicting data are available about T regulatory CD4+CD25+^{bright} FoxP3 cells. However, these cells were found to be increased in peripheral blood and CSF obtained from patients with active BS [78–80].

6.1.3.3 Cytokines and Chemokines

Proinflammatory cytokines. IL-1 has been found to be increased in sera from BS patients [81] and more recently the onset of disease has been correlated with single nucleotide polymorphisms (SNP) of IL-1 [82, 83]. Indirect data, based on efficacy of IL-1 inhibitors as therapeutic agents, indicate a possible pathogenetic role of this cytokine in BS. Conflicting results have been reported on TNF-α concentration in sera of BS patients. The spontaneous and LPS-stimulated production of TNF-α was significantly increased in patients with BS, however without any correlation with disease activity [84]. More recently, a remarkable up-regulation in vitro of TNFR II and IL-12Rβ1 expression was observed, being maximal in the presence of TNF-α [51]. At the moment, a growing evidence suggests that anti-TNF-α agents represent an important therapeutic approach for BS patients [85]. IL-6 levels were demonstrated to be related to disease activity in BS [86–88]. This cytokine seems to play a pivotal role, in particular, for central nervous system involvement, as demonstrated by high level detected in CSF. Elevated IFN-α serum levels (mostly product by pDC) have been found in BS patients and seem to correlate with disease activity [89].

Th1-related cytokines. Several studies demonstrate the important role of the classical Th1 cytokines IL-12 and IFN-γ in BS; in particular IL-12 and IFN-γ levels result to be increased in BS patients with ocular involvement and IFN-γ is also increased in aqueous fluid of anterior chamber in Behçet patients with uveitis [90–92]. Also IL-18 was demonstrated to be elevated in sera of BS patients and seems to correlate with disease activity [93, 94].

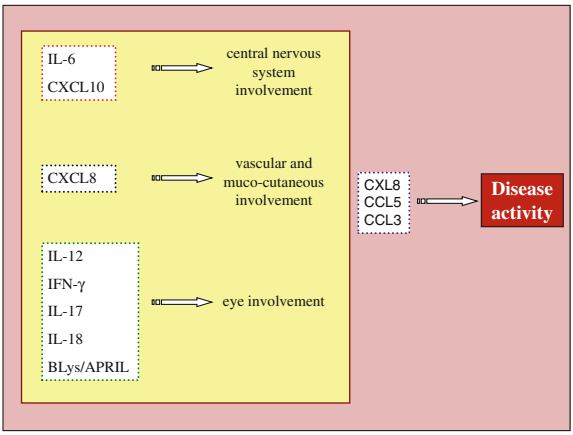

Fig. 6.2 Cytokine milieu, tissue damage and disease activity in patients with Behçet syndrome

Th17-related cytokines. As mentioned above, high levels of IL-17, IL-21, and IL-23 (cytokines critical for development, activation and function of Th17 cells) have been found in BS patients; in addition, IL-23 and IL-17A were reported to be elevated not only in peripheral blood, but also in aqueous fluid in patients with Behçet's uveitis [95].

Chemokines and chemokines receptors. CXCL8 (IL-8) was detected in high concentration in active BS patients and seem to correlate with vascular involvement [96, 97]. CXCL10 (IP-10) is an IFN-γ—induced protein; its levels result higher in CSF of NBS patients than in CSF of multiple sclerosis patients. Even though B lymphocytes do not seem to play a central role in the pathogenesis of disease, the B cell activating factors BLys/APRIL result overexpressed in the CNS of patients with NBS [98] and in patients with pulmonary and cutaneous manifestations [99, 100].

For the correlation between cytokines, involvement of different organs and disease activity see Fig. 6.2.

6.1.4 Immunopathology

BS is usually considered a systemic vasculitis. However, from an immune-hystological point of view BS patients have lesions with perivascular infiltrates (without involvement of blood vessel wall), mainly constituted by neutrophils and mononuclear cells, with a predominance of CD3+CD4+ T lymphocytes and NK cells [101, 102]. B cells are not found in significant number inside the lesions. Moreover, a high proportion of CD8+CD56+ (NKT cells) and CD3+CD8+ (cytotoxic T cells) has been found in the eye [103, 104]. More important, CD4+ T cell infiltrates with a Th1 phenotype have been reported to produce high levels of chemokines (CCR5, CXCR3) and cytokines (TNF-α, IFN-γ, IL-12) in oral, genital,

pseudofollicular and gastrointestinal lesions. In conclusion, the histopathological features are characterized by (a) systemic perivasculitis, (b) early neutrophil infiltration, (c) T cell infiltrates, (d) endothelial cell swelling, and (e) fibrinoid necrosis of blood vessel wall.

6.2 Global Scenario

The pathogenesis of BS appears tremendously complex; however, the main actors of this *scenario* are (1) a genetic background (HLA-B*51 and non-HLA), (2) the activation of both innate and adaptive immunity by pathogens, (3) the activation of T lymphocytes with a Th1 and Th17 phenotype, (4) an interaction between Th1 and Th17 with activated neutrophils, which together with lymphocytes are ultimately responsible for tissue damage in BS (see Fig. 6.3).

Pathogens can activate innate immunity (in particular neutrophils and $\gamma\delta$T cells) and acquired immunity (following antigen processing and presentation to naïve T lymphocytes by APCs). The first response is due to the recognition by $\gamma\delta$T cells (particularly expressed in the mucosa of patients with BS) of bacterial HSP largely homologous to human HSP, with non-MHC restricted mechanisms. Such

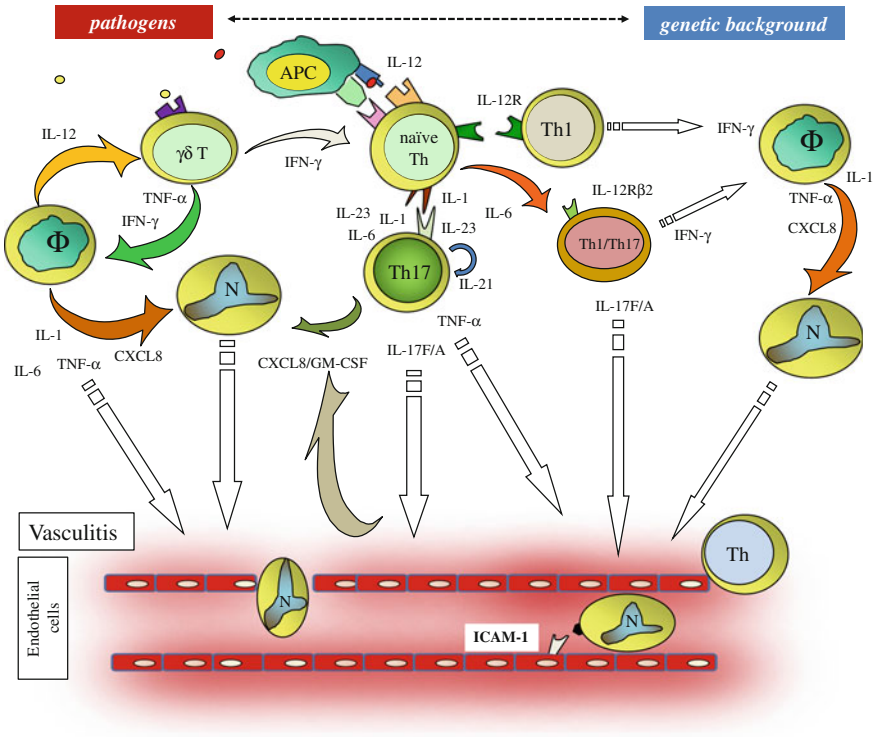

Fig. 6.3 Overview on Behçet syndrome pathogenesis

homology maintains the immune response with a mechanism of molecular mimicry. The $\gamma\delta$T cell activation leads to the production of TNF-α, but especially of IFN-γ, with consequent activation of macrophages capable of producing large amounts of IL-1, TNF-α and CXCL8.

On the other hand, antigen presentation by APC to naïve CD4+ T cells, in the context of MHC class II, leads to the production of IL-12, the most powerful cytokine inducing Th1 response. Some data also demonstrate the role of Th17 cells and their cytokines in BS pathogenesis. As well known, a combination of IL-6 or IL-1 with IL-23 is crucial for the differentiation of naïve T lymphocytes into Th17 cells; increased levels of IL-6 and IL-1 are documented in BS, while at the best of our knowledge, there are no data on the role of IL-23 in BS. However, recently it has been reported that the genes encoding for IL-10, IL-23 receptor (IL23R), and IL12Rβ could be novel BS susceptibility loci [105, 106]. IL23R is expressed on Th17 cells and macrophages, so IL23R gene polymorphisms might enhance responsiveness to IL23 in Th17 cells and other IL23R positive cells promoting BS development.

Furthermore, CD4+ T cells producing IL-21 are dramatically increased in the peripheral blood of patients with BS, and this cytokine is able to maintain the differentiation of Th17 cells [76]. On the other hand, the small percentage of Th17 cells in tissue infiltrates could be explained by their limited expansion in response to T-cell receptor triggering and to their capacity to shift to Th1 phenotype in the presence of IL-12 [107].

Neutrophils are, together with lymphocytes, the main effector cells in the pathogenesis of BS and are the first responsible of tissue damage. These cells in BS are characterized by an intrinsic hyperactivation (HLA-B*51-related), since they are prone to be activated by IL-1, TNF-α and CXCL8, mainly produced by macrophages, and by TNF-α, GM-CSF and CXCL8 produced by Th17 cells. CXCL8 acts on the recruitment and activation of neutrophils, which in turn are able to produce CXCL8, thus inducing an autocrine loop. Neutrophils cross the blood vessel wall through the process of rolling, firm adhesion and *diapedesis*. This phenomenon, induced by a genetic background and TNF-α and IL-1 overproduction, is facilitated by the overexpression of β-integrins on neutrophil surface and of intercellular adhesion molecule 1 (ICAM 1) on previously activated endothelium.

In patients with BS an increase of reactive oxygen species (ROS) has been demonstrated, responsible for tissue damage; CXCL10 is also able to recall neutrophils into inflammatory sites [108, 109], and this could explain the accumulation of these cells in the main and most typical disease manifestations, such as hypopyon, pseudofolliculitis, vascular thrombosis, and pathergy lesions.

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Mucocutaneous Involvement in Behçet's Syndrome

7

Umit Tursen

7.1 Introduction

Behçet's disease (BD) was first defined by Hulusi Behçet, a Turkish Professor of Dermatology, in 1937 as a triad of recurrent aphthous stomatitis, genital aphthae and relapsing uveitis [1]. During the ensuing 65 years multiple systemic associations of the disease including articular, vascular, gastrointestinal, cardiopulmonary, and neurologic involvement have become increasingly apparent [2–4]. Mucocutaneous features are the most common presenting symptoms of the disease; eye, vascular, pulmonary, gastrointestinal, and neurological involvement are the most serious [4].

7.1.1 Mucocutaneous Lesions in BD

7.1.1.1 Oral Aphthae

Oral aphthae are localized, painful, shallow, round to oval ulcers often covered by a gray fibromembranous slough and surrounded by an erythematous halo. They are seen as minor or major ulcerations, sometimes with herpetiform distribution at any site in the oral cavity. International study group criteria do not permit diagnosis in the absence of oral aphthae, and oral aphthae was seen in all patients with BD. The vast majority of mild cases presents with recurrent aphthous ulcerations of the oral mucosa which are usually the earliest and universal sign of the disease that are indistinguishable from common aphthae—canker sores in appearance and

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localization and has a yellowish necrotic base. This is frequently the first symptom and can precede the other manifestations of the syndrome by many years. Minor aphthous ulcers (<10 mm in diameter) are the most common type (85 %); major or herpetiform ulcers are less frequent (Fig. 7.1). Such mouth ulcers may be so painful that the patient is unable to eat during the attack. Aphthae may evolve quickly from a pinpoint flat ulcer to a large sore. In addition, intervals between recurrences range from weeks to months and typically may precede the onset of ocular, central nervous system, and some other systemic findings by many years. Smokers often experience a relapse of oral ulcers after quitting and nicotine replacement patches have been suggested to be useful in BD [2–8].

Recurrent oral aphthous ulcers of BD should be differentiated from those of recurrent oral ulcers due to other causes. The common causes of oral ulcer are trauma, recurrent aphthous stomatitis (RAS), infections including herpes simplex, syphilis, HIV, herpangina, primer herpetic gingivostomatitis, and hand-foot-mouth disease, mucocutaneous disease such as lichen planus and erythema multiforme, immunobullous disease including pemphigus and pemphigoid, squamous cell carcinoma, cyclic neutropenia, drugs, and systemic disorders. Systemic conditions presenting with "aphthous-like" lesions, including BD, have been shown in Table 7.1: oral ulcers may be a part of systemic lupus erythematosus, MAGIC syndrome, Reiter's syndrome, and Sweet's syndrome, or may be secondary to hematinic/nutritional deficiencies including iron, vitamin B12, folic acid, Coeliac disease and hematological diseases such as cyclic neutropenia and lymphoma. The ulcers of oral mucosa can be seen in inflammatory bowel disease, especially in Crohn's disease and, to a lesser extent, in ulcerative colitis [8–11].

Histopathologic examination of oral ulcers in BD has a nonspecific pathology with a variable infiltrate of lymphocytes, macrophages, and neutrophils at the base of the ulcer. Leukocytoclastic and lymphocytic vasculitis may be seen if the inflammation is severe. Reimer et al. showed that there is no difference between direct IF on oral aphthae in RAS compared to BD. They found that, compared to

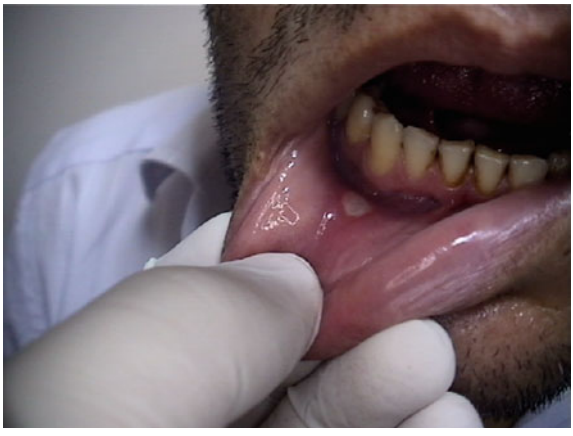

Fig. 7.1 Major oral aphthae

Table 7.1 Differential diagnosis of Behçet's mucocutaneous lesions

Manifestations	Treatments
Oral ulcers	Recurrent oral stomatitis
	PFAPA (periodic fever, aphthous ulcers, pharyngitis, adenopathy)
	Familial Hibernian fever
	Sytemic lupus erythematosus
	Ulcerative colitis
	Coeliac disease and other malabsorption states
	Iron, B12, and folate deficiency
	Human immunodeficiency virus infections
	Chickenpox
	Hand, foot and mouth disease
	Nicorandil (anal ulcers also reported)
	Bisphosphonates
	Cyclical neutropenia
	Lymphoma
	Bullous skin disease
	Syphilis
	Tuberculosis
	Lichen planus
Genital ulcers	Complex aphthosis
	Reiter's syndrome
	Mouth and genital ulcers with inflamed cartilage (MAGIC)
	Crohn's disease
	Sweet's syndrome
	Erythema multiforme
	Bullous skin disease
	Erosive lichen planus
	Fixed drug reaction
	CMV (in immunocompromised patients)
	Herpes simplex (HSV1)
	Chancroid
	Syphilis
	Scabies
	Tuberculosis cutis
	Munchausen syndrome
	Hypereosinophilic syndrome
	Myelodysplastic syndrome
	Acquired immune deficiency syndrome

(continued)

Table 7.1 (continued)

Manifestations	Treatments
Vasculitic ulcerations	Sweet's syndrome
	Pyoderma gangrenosum
	Erythema multiforme
	Erythema pernio
	Leukocytoclastic vasculitis
	Polyarteritis nodosa
Erythema nodosum	Crohn's disease
	Coeliac disease
	Colitis ulcerosa
Papulopustular eruptions	Acne vulgaris
	Folliculitis
Superficial thrombophlebitis	Erythema nodosum
	Lymphangitis
Pathergy positivity	Sweet syndrome
	Patients with chronic myeloid leukemia on treatment with interferon-α
	Erythema elevatum diutinum
	Pyoderma gangrenosum
	Inflammatory bowel disease including colitis ulcerosa and Chron disease
	Bowel bypass syndrome [9, 11]

nonaphthous oral lesions, oral aphthae of BD and RAS are characterized by C3 deposition in the vessel walls. IgM deposits also were detected in vessel walls in some patients in both groups [8, 9].

7.1.1.2 Genital Aphthae

In previous reports the prevalence of genital aphthae was found to be between 60 and 90 %. Genital lesions were most commonly seen on the scrotum of male patients and on the vulva of female patients and tended to be larger and deeper in the female patients, sometimes even leading to perforations. They occur usually on the scrotum in males and the shaft and glans penis may also be affected. The ulcers usually heal in 2–4 weeks; large ulcers frequently leave a scar whereas small ulcers and those on the minor labia heal without leaving a mark [2, 4, 7]. Genital ulcers are the second most commonly observed onset manifestation and resemble their oral counterparts. However, they are larger and deeper than mouth lesions, and appear at some time during the course of the disease [2, 4]. Genital ulcerations should be differentiated from venereal diseases such as syphilis, chancroid, and herpes simplex virus infection. Fix drug eruption, erythema multiforme, erosive lichen planus, autoimmune bullous dermatoses must be considered in the

differential diagnosis. Recurrent genital ulcerations may also be seen in Munchausen syndrome, hypereosinophilic syndrome, myelodysplastic syndrome, tuberculosis cutis, and acquired immune deficiency syndrome (Table 7.1). Because genital ulcers are occasionally asymptomatic, patient assessment should include examination of genitalia for ulcers and scarring, even when symptoms are absent. Histopathologic feature of genital ulcers of BD similar to that of oral ulcers [4, 9, 11].

7.1.1.3 Erythema Nodosum-Like Lesions

Erythema nodosum-like lesions are tender erythematous nodular lesions that appear more commonly on the anterior aspects of the lower extremities and slowly resolve within a few weeks without scar formation. The prevalence of erythema nodosum-like lesions was reported as 15–78 % with a higher frequency in females. Erythema nodosum-like lesions generally resolve in pigmented ethnic groups with residual pigmentation, but recurrence is common. These lesions may also occur at other sites, including the buttocks, upper extremities, and less commonly on the face and neck [2, 4]. Often, they have more erythema and edema around the lesions than the classic erythema nodosum. The lesions do not ulcer. A great variety of histopathological changes can be seen in typical, well-developed erythema nodosum in patients with BD. Authors have emphasized that the histopathological findings could be consistent with lymphohistiocytic septal panniculitis, lymphohistiocytic lobular panniculitis, granulomatous panniculitis, or acute necrotizing panniculitis [2, 11–14].

7.1.1.4 Papulopustular Lesions

Papulopustular lesions are situated mainly on the lower limbs and they are seen in as many as 34–70 % of patients with BD. In the literature, some of the papulopustular lesions of BD resembling the pustular lesions of acne vulgaris are called acneiform lesion of BD. The pathogenesis of pustular lesions of BD is different from those of acne vulgaris. The first one is a vasculitis while the second is a sebaceous gland disorder under hormonal factors. The pustular lesions of BD are located more often on the lower part of the body, while the pustules of acne vulgaris are seen more frequently on the upper part of the body. Some authors believe that they are the most common cutaneous manifestation, and their distribution is more widespread than adolescent acne, affecting face, limbs, trunk, and buttocks. Diri et al. showed that papulopustular lesions are seen more frequently in patients with BD with arthritis. Some authors have advised histologic confirmation that the papulopustular lesions are indeed vessel-based and neutrophilic. Some authors showed that there is a significantly higher frequency of papulopustular eruptions in males compared with females [2, 4, 12, 15]. Alpsoy et al. pointed out that the detection of nonfollicular lesions over the trunk or extremities, with the support of histopathologic and/or immunofluorescence studies, increases the specificity of these lesions [15]. Papulopustular lesions were included in the International Study Group Criteria as a result of their 70 % sensitivity and 76 %

specificity; whereas some authors stated that papulopustular lesions exhibiting vessel-based neutrophilic reaction and follicle-based lesions are both features of BD, and any papulopustular lesions, including follicular acneiform lesions, should be regarded as features of BD. Boyvat considering this argument, pointed out that papulopustular lesions of BD which have nonspecific features may create problems in the diagnosis of BD because they are extremely common also in the general population [16].

7.1.1.5 Superficial Thrombophlebitis

Superficial thrombophlebitis, which is one of the characteristics of BD, is represented as palpable, painful subcutaneous nodules or string-like hardenings with reddening of the overlying skin especially on the lower extremities. It is segmental and can present in a characteristic migratory pattern. Although it is transient, which disappears in a few days, it has a tendency to recure. In several studies thrombophlebitis was found to be present in 2.2–20 % of Behçet patients. The higher prevalence of thrombophlebitis in males is confirmed in previous reports [2, 4, 15]. Vena saphena magna is the most affected vein. It can be differentiated from erythema nodosum-like lesions, which may be similar clinically, by dermal ultrasonography: erythema nodosum-like lesions are hyperechoic on sonography, while the lesions of superficial thrombophlebitis are hypoechoic. It is important that, because of the relationship between superficial thrombophlebitis and deep venous thrombosis, close monitoring is required for the vascular systemic disease. On histopathologic examination, organized thrombus is observed in the vein lumen. Fibrous thickening of the vein wall and sometimes infiltration of mononuclear cells may be seen [4, 11].

7.1.1.6 Pathergy Test

One clinically unique feature of the disease is hyper-reactivity of the skin to any intracutaneous injection or needle prick, which is known as pathergy (Behcetine test). It is characterized by the formation of a sterile pustule or small papule 24–48 h after an intradermal needle prick [2, 4]. At 24–48 h, the puncture site becomes inflamed and the test is considered positive if there is an indurated erythematous small papule or pustule formation of more than 2 mm in diameter, which usually resolves within 3 or 4 days [2] (Fig. 7.2). There are controversies about the histopathology of the pathergy reactions. Some authors found mixed infiltration, while others reported neutrophilic infiltration with leukocytoclastic vasculitis [4, 11]. It was found high-pathergy positivity in the Mediterranean and Far Eastern countries (40–98 %) [2, 4]. However, test positivity is uncommon in individuals living in Western World, which reduces its diagnostic value in these countries [2]. The pathergy test is more strongly positive in male patients [4]. Pathergy test was usually found during active phase in Behçet's patients with positive reaction [4, 5]. However, the presence of a positive pathergy reaction is not associated with an increased risk for specific mucocutaneous or systemic manifestations of the disease, and does not predict a more severe disease course [4, 6]. Oral pathergy test was described by some authors like skin pathergy test [17, 18].

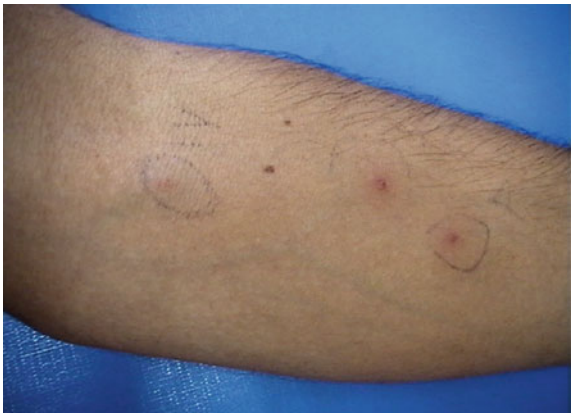

Fig. 7.2 Patergy phenomenon

Pathergy describes the inappropriately excessive subacute inflammatory reaction to nonspecific injury. It is relatively specific for BD, although it can also be observed in Sweet syndrome, in patients with chronic myeloid leukemia on treatment with interferon-α, erythema elevatum diutinum, pyoderma gangrenosum, and also inflammatory bowel disease such as colitis ulcerosa and Chron disease [2, 4].

The urat crystal test has been found to be more sensitive than the formal pathergy test in the demonstration of abnormal inflammation in BD. The usual response to an intradermal injection of 2.5 mg of urate crystals is an erythematous reaction, maximal at 24 h and mostly resolved at 48 h. In BD, the erythematous response is exaggerated, with a greater degree of inflammation present at 24 h and/or persistence at 48 h. This test has been reported as having a sensitivity of 61 % and a specificity of 100 % for the diagnosis of BD. The greater sensitivity of the urate crystal test suggests it has clear potential as an aid to the diagnosis of BD, although a positive test may be difficult to demonstrate in patients on anti-inflammatory drugs [18].

7.1.1.7 Other Skin Lesions

Other skin lesions, such as extragenital skin ulcers in the axillary and interdigital areas, Sweet's syndrome, pyoderma gangrenosum, leukocytoclastic vasculitis, palpable purpura, hemorrhagic bullae, furuncles, abscesses, erythema multiforme-like lesions, pernio-like lesions, polyarteritis-like cutaneous lesions, true arterial lesions, subungual infarctions, are less common [19–24].

Extragenital ulcers. Extragenital ulcers occur in about 3 % of patients. They are common in children with BD and these recurrent ulcers usually heal with mild scarring. Skin biopsies of extragenital ulcerations showed vasculitis. They are 20–30 mm in diameter with a yellowish necrotic base. The ulcers are recurrent and occur mainly on the internal part of the thighs, in the inguinal and axillary regions, but can affect neck, inframammary, and perianal areas, breast, legs, and interdigital area of the feet (Fig. 7.3). Extragenital ulcers look like aphthous ulcers and commonly heal leaving a round atrophic scar [5–9, 19].

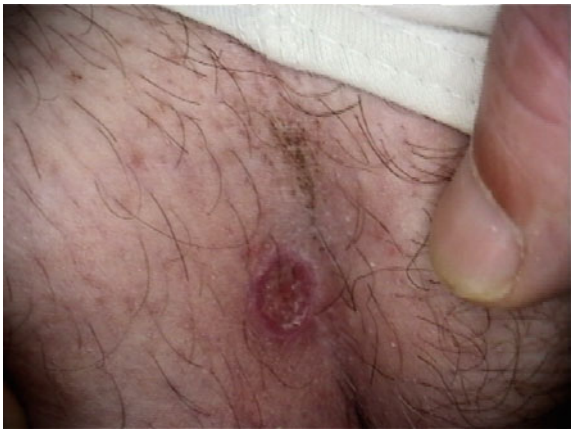

Fig. 7.3 Extragenital ulcers

Pyoderma gangrenosum. Pyoderma gangrenosum-like lesions are extremely rare. Pyoderma gangrenosum is a neutrophilic dermatitis with the same hypersensitivity to trauma as BD. In pyoderma gangrenosum some cases are associated with bowel disease as in BD. Also, pyoderma gangrenosum can produce in some cases localization of neutrophilic lesions in other organs such as heart, lymph nodes, and central nervous system which resembles BD to some extent [20].

Sweet's syndrome-like lesions. Sweet's syndrome-like lesions are rarely seen in patients with BD and, if present, are usually fewer in number. They are seen as painful erythematous nodules and plaques, associated with fever and leucocytosis. Sometimes, they may be pustular. Sweet syndrome-like lesions can be seen on the face, neck, and extremities. The lesions demonstrate neutrophilic infiltration, or perivascular and periadnexal inflammatory infiltrate of lymphocytes, histiocytes, and neutrophils in the dermis. In some cases, vasculitis may also be seen. Sometimes, Sweet's syndrome represents a flare of BD [25].

Necrotizing vasculitic ulcers. Some cases of BD with severe necrotizing vasculitis as a skin manifestation have been described. A case of BD in a 11-year-old Korean boy who had severe necrotizing vasculitis as a skin manifestation was reported [12]. Cutaneous vasculitis in BD is predominantly a venulitis or thrombophlebitis, with relative sparing of the arterial compartment. Chen et al. reported that approximately half (48 %) of BD patients with cutaneous lesions had either lymphocytic (31 %) or leukocytoclastic vasculitis (17 %). They have suggested that vascular inflammation is the pathologic basis of the skin lesions in BD and that the histologic spectrum ranges from fully developed necrotizing vasculitis with marked fibrinoid necrosis of vessel walls to perivascular inflammation with or without a marked interstitial infiltrate [13–15]. Plotkin et al. reported that a patient with chronic recurrent migratory superficial thrombophlebitis and marked cutaneous hyper-reactivity (pathergy) who developed leukocytoclastic vasculitis with recalcitrant leg ulcerations 9 years after the onset of his illness [16]. Cutaneous polyarteritis- nodosa-like lesions and necrotizing panarteritis involving small and medium-sized arteries in the dermis–subcutis junction have also been reported

rarely with BD. Vikas et al. reported that their patients had both venous and arterial involvement, the former with thrombotic angiopathy and the latter with acute vasculitis [17].

7.2 Diagnosis and Differential Diagnosis

In the absence of a universally accepted diagnostic test, the diagnosis of BD remains purely clinical. In 1990, the International Study Group for BD proposed new diagnostic criteria based on the analysis of 914 patients from several countries. For patients to be classified as having BD, the patients must have recurrent oral ulcers plus at least two of the other criteria including ocular involvement, genital ulcers, skin lesions (erythema nodosum-like lesions and papulopustular eruptions) or the pathergy test in the absence of an alternative clinical diagnosis. It is important to note that a patient who fails to meet the criteria fully may still have BD [26]. It usually is not difficult to recognize the full-blown syndrome of BD, but the so-called incomplete forms sometimes cause problems. Therefore, other causes of oculomucocutaneous syndromes should carefully be excluded including autoimmune bullous skin diseases, erythema multiforme major, Reiter syndrome, seronegative arthropathies, sarcoidosis, sweet syndrome, cicatricial pemphigoid, celiac disease, and pemphigus vulgaris. Similarly, herpes simplex virus infection, lichen planus, syphilis, systemic lupus erythematosus, ulcerative colitis, and mixed connective tissue diseases may also cause oral, cutaneous, and ocular lesions. Hughes-Stovin syndrome should also be differentiated and this syndrome consists of deep venous thrombosis often involving the caval vein accompanied by single or multiple pulmonary arterial aneurysms. Plausible alternative diagnoses such as seronegative arthropathies, rheumatoid arthritis, psoriatic arthritis, acute febrile neutrophilic dermatosis, familial Mediterranean fever, hyper IgD syndrome or periodic fever, pyoderma gangrenosum, multiple sclerosis, pulmonary embolism, and any cause of hemoptysis should be excluded. Oral ulcers alone should be differentiated from recurrent aphthous stomatitis, erythema multiforme, toxic epidermal necrolysis, syphilis, tuberculosis orificialis, inflammatory bowel diseases and erosive lichen planus. Genital ulcerations should be differentiated from venereal diseases such as chancroid, syphilis, scabies, and herpes simplex virus infection. Similarly, recurrent orogenital ulcerations are also seen in hypereosinophilic syndrome, myelodysplastic syndrome, Monchausen syndrome (pseudo-Behçet's syndrome), pemphigus vulgaris, tuberculosis cutis, and acquired immunodeficiency syndrome [2, 4, 9, 11] (Table 7.1).

7.3 Treatment of Mucocutaneous Lesions

In mild forms of the mucocutaneous disease, initial treatment consist of mild diet, and avoidance of hard, spicy, or salty nutrients and chemicals. Topical treatment of oral ulcers includes caustic solutions (silver nitrate 1–2 %, tinctura myrrhae

5–10 % w/v, hydrogen peroxides 0.5 %, methyl violet 0.5 %) 1–2x/day, topical antiseptic and anti-inflammatory drugs (amlexanox 5 % in oral paste, rebamipine, hexetidine 1 %, chlorhexidine 1–2 % mouthwash solutions, benzydamine, camomile extracts, tetracycline mouthwash) and also glycerine solution 250 mg/5 ml glycerine for 2 min, 4–6x/day, topical corticosteroids (triamcinolone mucosal ointment, dexamethasone mucosal paste, betamethasone pastilles) 4x/day or during the night or intrafocal infiltrations with triamcinolone suspension 0.1–0.5 mL/lesion, topical anesthetics (lidocaine 2–5 %, mepivacaine 1.5 %, tetracaine 0.5–1 % gels or mucosal ointments) 2–3/day, topical sucralfate (suspension, 1 gr/5 mL) 4x/day, 3 months durations as mouthwash, topical aminosalicylic acid (5% cream) 3x/day [27, 28]. In daily practice, the contents of a tetracycline capsule (250 mg) can be dissolved in 5 ml of water, holding in the mouth for about 2 min (four times a day). Behçet's disease patients with insufficient oral intake caused by pain can be treated with topical lidocaine (2–5 %) applications before meals and oral anti-inflammatory rinses containing chlorhexidine gluconate (1–2 %) [29].

In topical treatment of genital ulcers and cutaneous lesions, corticosteroid and antiseptic creams can be applied for a short period of time like 7 days. Painful genital ulcers can be managed by topical anesthetic in cream [29]. Topical sucralfate reduces the healing duration and pain of genital ulcers like oral ulcers. Sucralfate has been used in the treatment of orogenital ulcerations [30]. For severe ulcers, intralesional corticosteroid (triamcinolone acetonide) may be helpful. Corticosteroid injections like triamcinolone 0.1–0.5 mL/lesions can be focally applied in recalcitrant ulcerations [29]. Bacanli et al. studied the efficacy of topically applied granulocyte colony-stimulating factor in the treatment of oral and genital ulcers. It decreased the healing time and pain of both ulcers in 6 of 7 patients compared with the pretreatment period. The effectiveness of the treatment, however, did not continue during the posttreatment period [31]. In a randomized, controlled, crossover double-blind trial, zinc sulfate treatment decreased the mucocutaneous manifestations index after the 1 month of therapy. After shifting to placebo treatment, the clinical index started to increase but remained significantly lower than levels before therapy [32].

In severe forms of the mucocutaneous type of the disease, additional systemic treatment is required. The following drugs have proven beneficial: Corticosteroids (prednisolone, initial dose 30–60 mg/day p.o. for at least 4 weeks) can be administered as monotherapy or in combination with colchicine (1–2 mg/day p.o.), dapsone (100–150 mg/day p.o.), interferon-α (3–12 million IU/3x week s.c.), or azathioprine (initial dose 100 mg/day p.o.). Nonsteroidal anti-inflammatory drugs like indomethacin (100 mg/day p.o. over 3 months) can be effective on the mucocutaneous lesions. Pentoxifylline (300 mg 1-3x/day p.o.) and oxypentifylline (400 mg 3x/day p.o.) treatment for 1 month induced a remission of oral ulcers. Pentoxifylline decreases superoxide production by neutrophils. High dosage of oral or pulse intravenous steroids may be indicated for large and refractory mouth ulcers larger than 10 mm or when the oropharynx is compromised. Severe mucocutaneous disease and arthritis may be treated with systemic corticosteroids in combination with azathioprine [33–41].

Colchicine (0.5–2 mg/day p.o.) can be used as a second-line alternative treatment. A recent randomized double-blind and placebo controlled study has shown that colchicine reduces the occurence of genital ulcers and erythema nodosum among women. Colchicine inhibits the enhanced chemotactic activity of neutrophils. Colchicine seldom eliminates oral ulcerations completely, but may reduce to an acceptable level the frequency and severity of oral ulcer [38].

There is little evidence that antibacterials or antivirals are useful in the therapy of mucocutaneous lesions. There is some evidence that adjunctive penicillin treatment may enhance the clinical response to colchicine therapy for both oral and genital ulcers [42]. It has been proposed, although not proven, that an etiologic relationship exists between streptococcal infection and BD. In an uncontrolled study, benzathine penicillin improved the clinical manifestations of disease. Patients with mucocutaneous lesions had complete recovery in 5–20 days. In a retrospective study, benzathine penicillin had a beneficial effect on oral and genital ulcers. However, no meaningful effects were seen on other lesions. A prospective randomized study compared the efficacy of colchicine with colchicine and benzathine penicillin over 24 months. The number of arthralgia episodes was significantly reduced in the combination group and episode-free period was significantly prolonged with combination therapy. And they reported the effectiveness of benzathine penicillin and colchicine on the mucocutaneous manifestations, benefits not achieved with colchicine monotherapy [42, 43]. The result of an open study with minocycline treatment for 3 months was reported and it was observed that orogenital ulcers, erythema nodosum, and papulopustular eruptions improved at a rate of 10–100 % [44]. We already reported that erythromycin treatment appears to be an effective treatment option in erythema nodosum-like lesions in BD. The hypothetical anti-inflammatory effects of erythromycin, besides its antibiotic properties, explain such a clinical improvement [45].

Dapsone (100–150 mg/day p.o.) also inhibits the enhanced chemotactic activity of neutrophils and can be used as an alternative drug to colchicine. Quick relapses have been found after discontinuation of dapsone treatment. Intermittent ascorbic acid treatment (vitamin C; 500 mg/day) is advisable to prevent increased methemoglobin serum levels. Its use is often complicated by hemolytic anemia, even in patients with normal glucose-6-phosphate-dehyrogenase activity [34].

Interferon-α has been successfully used in the treatment of BD. Its immunomodulatory effect, ability to augment the decreased activity of the patient's natural killer cells, capacity to inhibit neovascular proliferation, and antiviral activity have been suggested to explain its action in BD. It was shown to markedly inhibit CXCL8 synthesis and secretion form endothelial cells. Interferon-α-2a treatment at dose of 6 million IU/3 10 week s.c. for 3 months, is an effective alternative treatment, particularly for management of mucocutaneous lesions [46].

Azathioprine (2.5 mg/kg body weight/day p.o.) has been found to be an effective choice in oral and genital ulcers in a randomized, double-blind, and placebo controlled study [47].

Cyclosporin A (3 mg/kg/day p.o.) is capable of markedly ameliorating mucocutaneous lesions. But, it should be reserved for the most severe patients because of its significant long-term adverse effects [48].

Methotrexate (7.5–20 mg/1x weekly p.o. over 1 month) is able to induce an improvement of a severe mucocutaneous involvement [49].

Thalidomide (100–300 mg/day orally., optimal dose 100 mg/day in the evening for 8 weeks) has been approved for the treatment of male and sterilized or postmenapausal women with BD. Thalidomide was shown to selectively inhibit TNF-α synthesis by monocytes. In a randomized, double-blind placebo controlled study with 63 patients with BD, a remission of oral and genital ulcers, as well as papulopustular eruptions was detected in 24 % of the patients over 2 months. During the 6 months treatment, 30 % of the patients with BD remained free of mucocutaneous lesions. Discontinuation of the treatment results in oral and genital ulcers recurrences; therefore a maintenance treatment with 50 mg/day to 50 mg twice a week is recommended. Thalidomide is often highly effective at reducing the frequency and severity of mucocutaneous disease resistant to colchicine. However, its widespread use is clearly limited teratogenic and neuropathic complications. The risk of developing irreversible peripheral neuropathy is thought to increase in a dose-dependant fashion, and so thalidomide should be recommended at the lowest dose possible to control symptoms, e.g., 50 mg daily or 100 mg 3 times a week. Since thalidomide can be sedating, it is best taken at night [50–52].

Recent studies of anti-TNF agents such as infliximab (i.v. 0, 2, 4, 8. months), and etanercept (s.c. twice a week) have shown favorable results [53, 54].

Lactobacilli, which have anti-inflammatory activity, may be useful in some diseases, particularly in inflammatory bowel disease. In a study aimed at evaluating the efficacy of lactobacilli lozenges in the management of oral ulcers of BD, a significant decrease in the mean number of ulcers was found following treatment, especially among women [55].

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Neurological and Neuropsychological Manifestation in Behçet's Syndrome

8

Shunsei Hirohata

8.1 Introduction

Behçet's syndrome (BS) is a chronic relapsing inflammatory disease, characterized by the recurrent episodes of remission and exacerbation of various symptoms, including aphthous stomatitis, uveitis, genital ulcers, and skin lesions, whereas chronic sustained inflammation in certain tissues is rare [1]. Although its etiology remains unclear, there are common characteristic histopathological features in the inflamed tissues, such as perivascular infiltration of lymphocytes and monocytes, and sometimes polymorph nuclear leukocytes, without microscopic changes in the vessel walls. Thrombophilia or thrombophlebitis involving small and large veins is also common, whereas arteritis is rare. In these regards, BS is different from other vasculitides [1].

Among various manifestations, posterior uveitis attacks usually result in the loss of vision that seriously affects the activity of daily life of the patients. Furthermore, vascular involvement, intestinal involvement, and central nervous system (CNS) involvement are usually life-threatening, and therefore require aggressive treatment [1].

The CNS involvement in BS is either caused by primary neural parenchymal lesions (neuro-Behçet's syndrome [NB]) or is secondary to major vascular involvement, such as cerebral venous thrombosis (CVT) [2, 3]. CVT in BS is rarely complicated with the parenchymal lesions and should be called vasculo-Behçet's syndrome [2]. The CVT generally has a better prognosis compared with the parenchymal type CNS involvement [2].

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In NB, involvement of brainstem is the most common, whereas spinal cord involvement, cerebral hemispheric involvement, and meningoencephalitis also occur [3–5]. The etiology and pathogenesis of NB remain unclear. Moreover, factors determining prognosis, reliable diagnostic tools and appropriate treatment regimens have not been delineated. The majority of patients with NB had only single attacks, whereas one-third of patients presented further attacks [3–5]. On the other hand, a number of studies have reported the presence of patients who underwent progressive deterioration leading to disability (primary or secondary progressive course) [3–5]. Furthermore, recent studies have disclosed that NB can be classified into acute NB and chronic progressive (CP) NB depending on their differential clinical courses, especially on their differential responses to steroids [6–8]. Thus, acute NB responds well to corticosteroid and is usually self-limiting, whereas CP NB presents intractable, slowly progressive neurobehavioral changes and ataxia in spite of high doses of steroids [6–8]. In addition, increasing attention has been paid to the effect of anti-tumor necrosis factor alpha (TNF-α) therapy in BS, including NB [1]. The present article overviews an update on the neuropathogenesis, clinical manifestation, and treatment of NB, and also suggests potential new therapeutic options.

8.2 Clinical Manifestations

8.2.1 Cerebral Venous Thrombosis

CVT is seen in 10–20 % of patients with neurologic involvement [5, 8–10]. Thrombosis of the venous sinuses may result in increased intracranial pressure with headache, papilledema, cranial nerve palsies, and mental changes [5, 8–10]. CVT in BS occurs relatively slowly in most cases, but acute onset with seizures and focal neurologic symptoms is also possible [11]. Superior sagittal sinus is most frequently involved. The occurrence of CVT together with primary CNS parenchymal involvement in the same patient is rare [8, 10, 12]. CVT in BS is strongly associated with systemic major vessel disease, such as thrombosis of major veins and pulmonary artery aneurysm, and should therefore be regarded as vasculo-Behçet's syndrome [10, 13, 14]. Overall, patients with CVT have a better neurological prognosis than the patients with neuroparenchymal NB, as recurrence and neurologic deficits are less likely to occur. However, due to the increased association with major systemic vessel disease, they may have a higher overall morbidity and mortality, and therefore may not be always associated with a favorable outcome [4].

In a multicenter retrospective cohort study of BD patients who showed neurological manifestations between 1988 and 2008, only 1 of the 144 patients showed cerebral CVT, confirming that the incidence of CVT in Japan is much lower that that in the middle-east or European countries [2–5, 15]. The reason for the paucity of CVT in Japan remains unclear. It is suggested that some ethnic differences in genetic factors might be involved, as in the case of intestinal involvement, which is much more common in the Japanese population [1].

8.2.2 Parenchymal Involvement (NB)

8.2.2.1 General Remarks

One of the most prominent characteristics in NB is a preference for involvement of brainstem-diencephalon and pontobulbar region [2]. Consistently, motor symptoms, cerebellar symptoms, brainstem symptoms, and dysarthria are frequently seen [4]. It should be noted that behavioral symptoms are seen in approximately 10 %. Although headache is the most common symptoms in NB [4, 16], it is also a common symptom in BS independent from neurologic involvement [16]. As to the neurological signs, pyramidal tract signs are most common and found even in the absence of apparent motor dysfunctions [2, 3].

The differential diagnosis of NB includes many CNS diseases, among which multiple sclerosis is one of the leading misdiagnoses. MRI findings indicate that the major lesion is located in the brainstem-diencephalon-basal ganglion region in NB [5]. However, the predominant lesion may be in the periventricular white matter in some cases, where it will be difficult to discriminate from multiple sclerosis. In such cases, cerebrospinal fluid (CSF) pleocytosis with polymorphonuclear predominance [5], the absence of more than two oligoclonal IgG bands [6], and the elevation of CSF IL-6 [1] may indicate NB. Within patients of BS, differential diagnosis should include isolate headache syndromes, cardiogenic embolic stroke, astrocytoma, meningioma, and syringomyelia [4]. In addition to careful clinical evaluation, the diagnostic values of CSF and magnetic resonance imaging (MRI) should be recognized.

We have recently disclosed that NB can be classified into acute type and CP type based upon clinical courses and responses to treatment [6, 15]. Consistently, Akman-Demir et al. proposed the subsets of NB, including attack(s) and remission, secondary progression, primary progression, and silent neurological involvement [5]. Attack(s) and remission in their series are considered to correspond to acute type, whereas primary and secondary progression should be the same as CP type in our classification [6, 15]. Thus, most of our patients with CP NB had preceding history of acute attacks [6, 15]. It is also possible that some patients with silent neurological involvement might be a modest form of acute NB, which represents preceding symptoms of primary progressive courses [5, 6, 15].

8.2.2.2 Acute NB

Acute NB is characterized by acute meningoencephalitis with or without focal neurological deficits, presenting high intensity areas in T2-weighted images or fluid attenuated inversion recovery (FLAIR) images on MRI scans [15] (Fig. 8.1). Among a variety of neurological manifestations, headache and fever were more common in acute NB (Table 8.1) [15]. Acute NB responds to corticosteroid therapy, and is usually self-limiting, although recurrence of the attacks is sometimes seen. It should be noted, however, that there are still patients with high degree of permanent damage or disability due to acute type attacks [4, 5, 17]. Cyclosporin A is frequency associated with acute NB, at least among the Japanese patients [18].

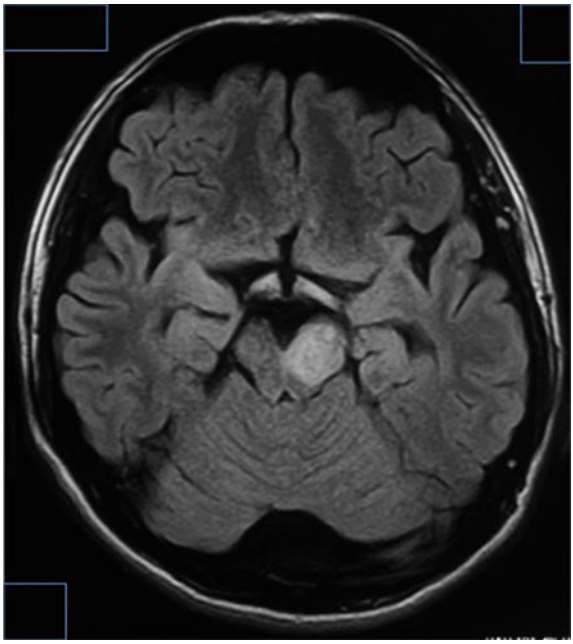

Fig. 8.1 Axial fluid attenuated inversion recovery (FLAIR) brain MRI of a patient with acute NB, showing high density lesions in the left midbrain

8.2.2.3 Chronic Progressive NB

The CP type of NB is characterized by intractable, slowly progressive neurobehavioral changes with neurological deficits, leading to severe disability and deterioration [1, 4]. Thus, ataxia, dysarthria, urinary incontinence, and neurobehavioral symptoms were more frequently observed in CP NB (Table 8.1) [6, 15]. The neurobehavioral changes include cognitive dysfunction, euphoria, loss of insight, disinhibition, indifference to their disease, psychomotor agitation or retardation, with paranoid attitudes and obsessive concerns [4]. These symptoms should not be confused with psychosis associated with the use of corticosteroid or other therapy. Of note, the patients with CP NB show persistent marked elevation of CSF IL-6 (>20 pg/ml) with very modest increase in cell numbers and total protein [6]. The most characteristic findings on MRI include atrophy of brain stem and cerebellum in CP NB (Fig. 8.2). Most patients (approximately 90 %) in our series with CP NB were HLA-B51-positive, and they had history of attacks of acute NB prior to the development of progressive neuropsychological symptoms [6]. Recently, it has been disclosed that HLA-B51 and cigarette smoking, and especially their combination, are risk factors for CP NB [19]. It is likely that certain substances in cigarettes might be immunogenic in the context of HLA-B51, resulting in the persistent activation of immune responses within the CNS in NB [19]. Of note, CP NB is resistant to conventional treatment with corticosteroid, with cyclophosphamide, or with azathioprine [6, 20]. Recent studies, however, suggest the efficacy of low-dose weekly MTX in the CP NB [20], as will be discussed later.

Table 8.1 Clinical symptoms in 144 patients with BS

n	Acute NB (%)	Chronic progressive NB (%)	Non-NB (%)	*p* value[a]
	76	35	33	
Headache	41 (53.9)	2 (5.7)	14 (42.4)	<0.0001
Fever	43 (56.6)	1 (2.9)	3 (9.1)	<0.0001
Neurobehavior/cognitive symptoms	7 (9.2)	18 (51.4)	3 (9.1)	<0.0001
Alteration of consciousness	7 (9.2)	1 (2.9)	5 (15.1)	0.2088
Ataxia	9 (11.8)	17 (48.6)	10 (30.3)	0.0001
Dysarthria	14 (18.4)	15 (42.9)	3 (9.1)	0.0019
Focal symptoms (motor, sensory, etc.)	20 (26.3)	7 (20.0)	10 (30.3)	0.6136
Bladder bowel disturbances	2 (2.6)	6 (17.1)	2 (6.1)	0.0208
Dizziness	0	2 (5.7)	4 (12.1)	0.0123
Vertigo	8 (10.5)	0	3 (9.1)	0.1429

[a]Statistical significance was evaluated by Chi square test (from [15])

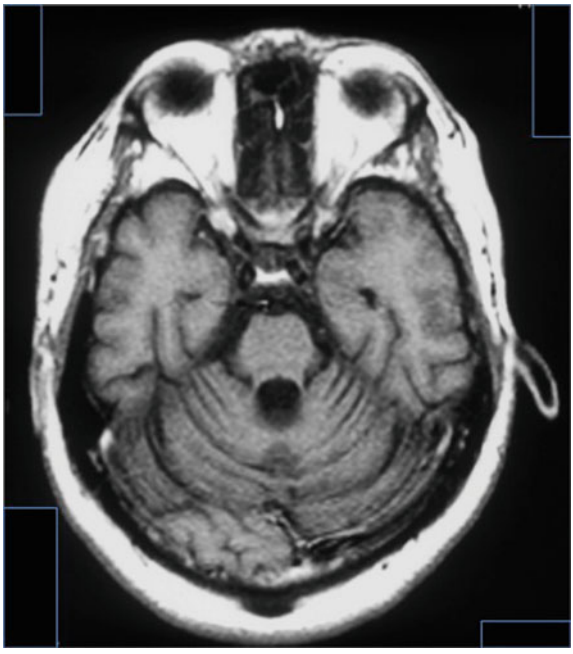

Fig. 8.2 Axial fluid attenuated inversion recovery (FLAIR) brain MRI of a patient with CP NB, showing atrophy of brainstem and cerebellum

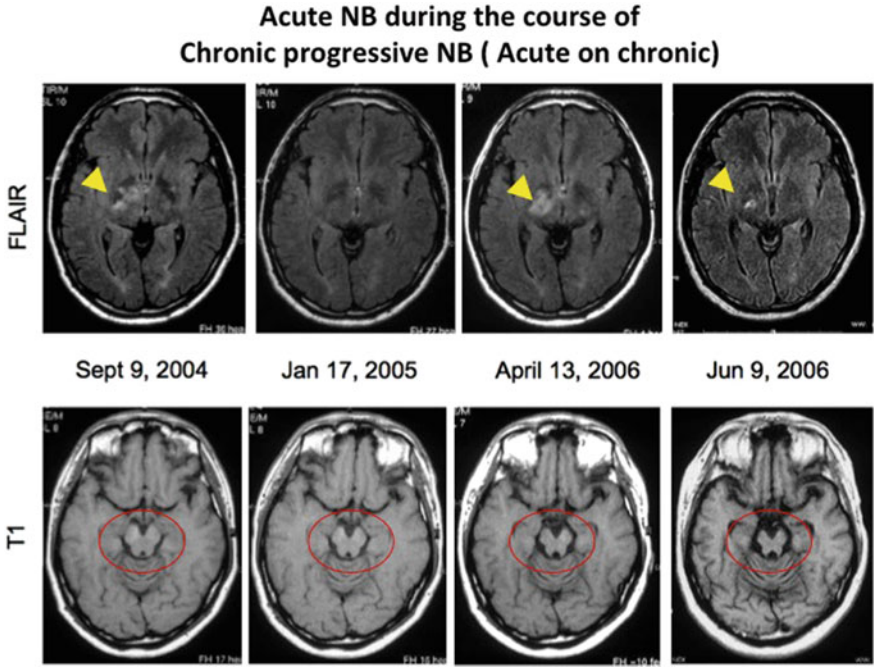

Fig. 8.3 Clinical course and changes in laboratory data of a patient who showed an attack of acute NB during the course of chronic progressive NB (from [21])

8.2.2.4 Acute NB During the Course of CP NB (Acute on Chronic)

It remained uncertain whether these two types of NB be independent clinical entities or represent different stages of the disease. In fact, some patients displayed prolonged elevation of CSF IL-6 activity following acute NB, leading to the development of CP NB [6]. However, we have recently experienced 2 patients who developed attacks of acute NB during the course of CP NB (acute on chronic) [21]. Notably, although the patients recovered from acute NB after treatment with corticosteroids, he continued to show manifestations of CP NB with continuous progression of brainstem atrophy (Fig. 8.3) [21]. It is therefore strongly suggested that acute NB and CP NB are different in their pathogenesis.

8.3 Histopathology and Immunological Disorders

We have previously delineated the characteristics of histopathology of acute NB, CP NB, and NB in a long-term remission at autopsy [22]. In acute NB, histopathology of the lesions revealed perivascular infiltration of mononuclear cells around small vessels (Fig. 8.4a), consisting mainly of CD45RO+ T lymphocytes and CD68+ monocytes with few CD20+ B lymphocytes. Of interest, Tunnel

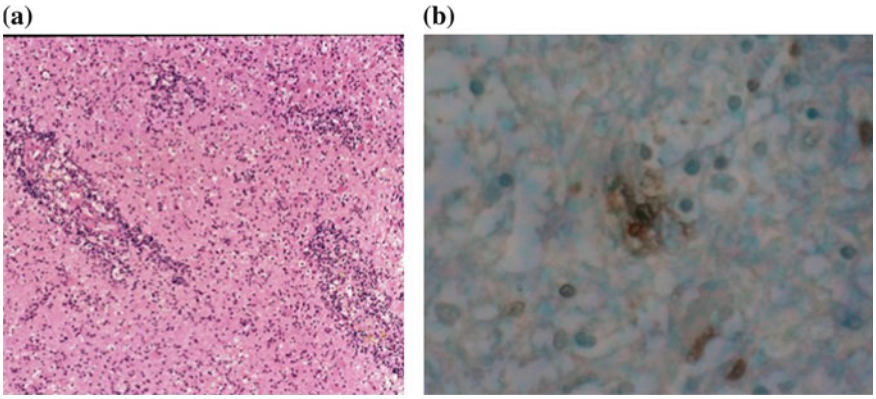

Fig. 8.4 Histopathology of lesions in the brain in acute NB. **a** Hematoxylin and eosin staining. **b** Tunnel staining

staining disclosed that most neurons were undergoing apoptosis in the inflammatory lesions with the formation of a binucleated neuron (Fig. 8.4b) [22]. In CP NB, the histopathological changes were basically similar to those in acute NB. Thus, perivascular cuffing of CD45RO+ T lymphocytes and CD68+ monocytes was noted in pons, cerebellum, medulla, internal capsule, and midbrain, although the degree of infiltration was less marked than that in acute NB. There were also scattered foci of neurons undergoing apoptosis with formation of a few binucleated neurons [22]. Finally, the most prominent feature of NB in a long-term remission after the attacks of acute NB was atrophy of basal pons with formation of cystic or moth-eaten lesions, consisting of isomorphic gliosis with viable neurons. There were still scattered foci of perivascular cuffing of T lymphocytes and monocytes [22]. These results emphasize the common features throughout the courses of NB, perivascular cuffing of T lymphocytes and monocytes, irrespective of the clinical phenotypes. More importantly, it is suggested that soluble factors produced by infiltrating cells, such as IL-6, might play a role in the induction of apoptosis of neurons in NB.

8.4 Diagnosis

8.4.1 MRI Findings

High intensity lesions on FLAIR images or T2-weighted images of MRI have been shown to be frequently observed in NB, especially in brainstem-diencephalon and pontobulbar regions [23]. Accordingly, in our retrospective multicenter cohort study with 76 patients with acute NB, 35 with CP NB, and 33 with non-NB, high intensity lesions were frequently seen in pons, midbrain, and basal ganglia in acute NB as well as CP NB [15]. However, there was no significant difference in the

frequencies of the occurrence of FLAIR or T2 high intensity lesions among acute NB, CP NB, and non-NB. Thus, these high intensity lesions were observed in as many as 42.4 % of non-NB patients, but as few as 60.5 % of acute NB patients [15]. Therefore, it is evident that inclusion of such abnormal MRI findings for the diagnostic criteria of acute NB results in reduced sensitivity and specificity. By contrast, brainstem atrophy was significantly more frequently observed in CP NB (71.4 %) than in acute NB (7.5 %) or non-NB (9.0 %), indicating that brainstem atrophy is a frequent and specific finding in CP NB and therefore can be included in the diagnostic criteria [15].

8.4.2 CSF Findings

Efficacy of CSF analysis in the diagnosis of NB has been poorly explored in the literature [3, 5]. Thus, with a limited number of patients, CSF constituents have been shown to be altered in only around 70–80 % of patients with parenchymal NB [9]. In our retrospective multicenter cohort study, CSF cell counts were significantly elevated in acute NB compared with non-NB and CP NB. Although CSF cell counts were also significantly elevated in CP NB compared with non-NBD, they were within normal limit in approximately 15 % of CP NB [15]. Modest but significant increase in CSF total protein as well as decrease in CSF glucose level was observed in acute NB and CP NB compared with non-NB [15].

Recently, increasing attention has been paid to CSF cytokines, especially IL-6 in NB. Thus, CSF IL-6 has been shown to be increased in patients with relapsing-remitting NB (acute NB) as well as in those with progressive NB (CP NB) [6, 24–28]. Consistently, CSF IL-6 was elevated in acute NB as well as in CP NB, but not in non-NB in our retrospective multicenter cohort study, although CSF IL-6 was examined only in 40 % of patients [15].

8.4.3 Diagnostic Criteria

In order to generate the diagnostic criteria for acute NB and CP NB, receiver operating characteristic (ROC) analysis of various parameters was carried out to examine their suitability for inclusion in the criteria. The sensitivity and specificity of CSF cell count for diagnosis of acute NB versus non-NB were 97.4 and 97.0 %, respectively, at the cut-off value of 6.2/mm^3 (Fig. 8.5a), whereas the sensitivity and specificity of CSF cell count for diagnosis of CP NB versus non-NB were 68.6 and 97.0 %, respectively, at the cut-off value of 6.0/mm^3 [15].

It should be noted that CP NB often follows the episodes of acute NB [5, 6]. It is therefore important to discriminate CP NB from recovery phase of acute NB. The sensitivity and specificity of CSF IL-6 for diagnosis of CP NB from recovery phase of acute NB were 92.0 and 94.7 %, respectively, at the cut-off value of 16.55 pg/ml (Fig. 8.5b) [15].

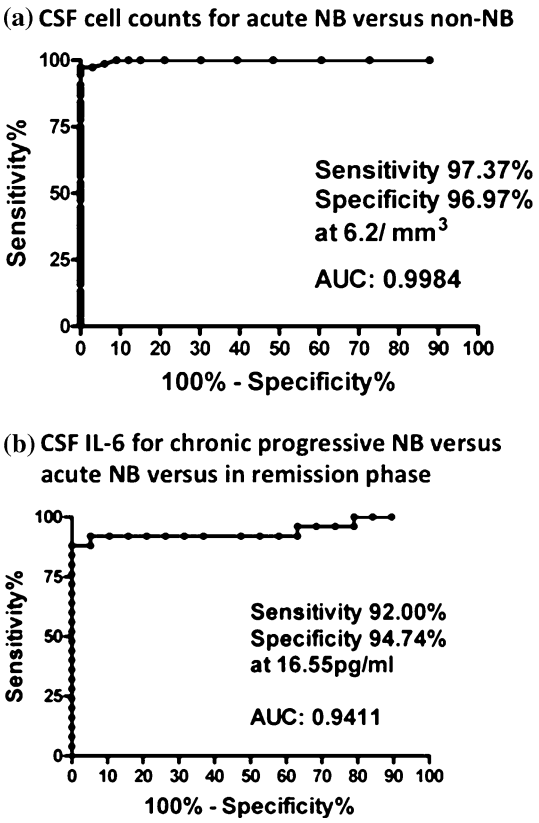

Fig. 8.5 Receiver operating characteristic (ROC) analysis of CSF cell count and CSF IL-6 for differential diagnosis of NB. **a** ROC analysis of CSF cell count for differential diagnosis of acute NB from non-NB. Area under the curve [AUC] **b** ROC analysis of CSF IL-6 for diagnosis of CP NB versus acute NB in recovery phase (modified from [15])

These results confirm that CSF IL-6 was a useful tool for diagnosis of CP NB in BS patients who showed neurological manifestations of insidious onset, whereas CSF cell count was a sensitive and reliable marker for diagnosis of acute NB in BS patients who showed neurological manifestations of acute or subacute onset. Since CSF IL-6 and cell count have been found to be elevated in CNS infections, it is necessary to rule out such conditions, especially in acute NB. Based on these findings, the diagnostic criteria for acute NB and CP NB are proposed, as shown in Table 8.2 [15].

8.5 Treatment

Treatment of NB may be different depending on its presentation: acute NB and CP NB. As to acute NB, treatment of active phase manifestations as well as prevention of another attack should be considered separately [4].

8.5.1 Acute NB

8.5.1.1 Active Phase Manifestations

Corticosteroids are widely used to treat active phase in acute NB, but their effects are short-lived and they do not prevent further attacks or progression [9]. Accordingly, more than 80 % of the patients with acute NB were treated with corticosteroids during the acute attacks in our retrospective multicenter cohort [15]. The patients are usually treated with oral prednisolone (1 mg/kg for up to 4 weeks, or until improvement is observed) with or without high-dose intravenous methylprednisolone (1 g/day) for 3–7 days [29]. After the attacks subside by treatment the doses of corticosteroids should be tapered over 2–3 months in order to prevent early relapses [29]. Although high dose intravenous methylprednisolone has been suggested to result in earlier improvement, there has been no controlled study to demonstrate its efficacy.

In addition to corticosteroids, the efficacy of interferon alpha (IFN-α) has been implicated in the treatment of the active phase manifestations of acute NB [30]. Thus, IFN-α2a might be effective in the treatment of acute NB as well as ocular manifestations, although further controlled study is required to confirm this point.

Recent clinical trials have demonstrated that infliximab is effective in suppressing the frequency of ocular attacks, and has favorable implications for the visual prognosis of patients with refractory uveoretinitis [31, 32]. Accumulating reports have also suggested the efficacy of infliximab for recalcitrant acute NB [25, 33].

Table 8.2 Proposed preliminary diagnostic criteria for classification of NB

Acute NB
1. Fulfilling the ISD criteria for BS
2. Acute or subacute onset of neurological symptoms, including headache, fever with or without any focal signs
3. Increase in CSF cell number over 6.2/mm^3
*The diagnosis of acute NB requires all the above items 1–3
Exclusion: infections of the central nervous system
Chronic progressive NB
1. Fulfilling the ISD criteria for BS
2. Insidious onset of neuropsychiatric symptoms, including dementia/neurobehavioral changes, ataxia, dysarthria with or without other manifestations
3. Presence of one of the following
a. Increase in CSF IL-6 over 16.55 pg/ml on two different occasions with intervals of at least 2 weeks
b. Increase in CSF IL-6 over 16.55 pg/ml and the presence of brainstem atrophy on MRI
*The diagnosis of chronic progressive NB requires all the above items 1–3

*indicates the key for diagnosis
From [15]

Thus, an improvement in symptoms was noticed within 24 h after receiving the first infusion and remained stable throughout the observation period with a complete resolution of signal abnormalities on brain MRI [33]. A similar patient with brainstem lesions in acute NB has been reported to respond well to infliximab [25].

On the other hand, it should be pointed out that the neurological involvement of acute NB sometimes subsides spontaneously [34]. Taken together, the use of corticosteroid, IFN-α and infliximab should be considered depending on the severity and the course of the neurological manifestations of patients with acute NB, since spontaneous remission might occur in some patients. Thus, careful evaluation of the severity of neurological attacks would be important.

8.5.1.2 Prevention of Relapse

Colchicine, azathioprine, cyclosporin A, cyclophosphamide, MTX, chlorambucil, and immunomodulatory agents such as IFN-α, pentoxyphilline and thalidomide have been anecdotally shown to be beneficial in preventing the occurrence of the systemic manifestations of BS, but none of these agents have been shown to be effective in preventing the attacks of acute NB in a properly designed study [4, 8, 9]. Cyclosporine A has been reported to result in neurotoxicity or to accelerate the development of CNS symptoms, and therefore its use in NB is not recommended [4, 8, 18].

8.5.2 Chronic Progressive NB

Addition of immunosuppressive drugs, such as azathioprine, oral, or intravenous cyclophosphamide to high doses corticosteroid has been usually performed in progressive NB; however, the efficacy of such a combination has also not been demonstrated to date [4–6]. It is now apparent that high doses of corticosteroid are not effective in CP NB [6]. Thus, the patients usually show exacerbation along with the elevation of CSF IL-6 activity even when higher doses of corticosteroid are used [6]. Neither cyclophosphamide, given orally or intravenously, nor azathioprine has been shown to prevent progression [6].

We happened to encounter a patient with CP NB, who dramatically responded to low-dose weekly MTX with marked decrease in CSF IL-6 activity. An open trial with 6 patients with CP NB showed that the neuropsychological manifestations as well as the findings on MRI scans and intelligence quotients were not significantly worsened after the trial [20]. Three patients presented with mild liver dysfunction, which returned to normal by decreasing the dose of MTX. Further studies performed to investigate the efficacy and the safety of low-dose weekly MTX for a longer period (4 years) confirmed its beneficial effects in CP NB [35]. Thus, these results indicate that low-dose weekly MTX therapy might be tolerable and have a beneficial effect in the treatment of patients with CP NB, since it prevented the progression of the neuropsychiatric manifestations by significantly decreasing CSF IL-6 levels. It should be emphasized, however, there are still a fraction of patients with chromic progressive NB, who did not adequately respond to MTX [35].

Of note, it has been reported that infliximab was effective for the treatment of long-standing CP NB [36, 37]. We also examined the efficacy of infliximab in 5 patients with CP NB refractory to MTX. These patients were given intravenous infusion of 5 mg/kg infliximab at weeks 0, 2, 6, and 14 with MTX (10–17.5 mg/week) and prednisolone (<10 mg/day). In all the 5 patients, CSF IL-6 were markedly decreased by 1/2–1/37 on the next day of the 1st infusion and remained below 20 pg/ml before the last infusion at 14 weeks, whereas CSF TNF-α were not significantly changed at any time point [38]. At 24 weeks from the initial infusion, none of the 5 patients showed exacerbation (3 patients significantly improved) without the progression of the atrophy in midbrain, pons and medulla on brain MRI scans [38]. Adverse effects occurred in 2 of the 5 patients, including transient headache in 1 patient and suspected subclinical pneumocystis pneumonia in the other patient [38]. These results suggest that infliximab might have a beneficial effect in the treatment of progressive NB by reducing CSF IL-6 levels but not TNF-α. Moreover, the rapid fall of CSF IL-6 after the infusion suggest that infliximab might directly act on inflammatory cells producing IL-6, presumably activated monocytes [38, 39]. It should be noted that etanercept, a recombinant TNF receptor Fc fusion protein, is also now being used in BS. Thus, recent studies have demonstrated that etanercept was effective in suppressing most of the mucocutaneous manifestations in BS [40]. Therefore, clinical trials to explore the efficacy of etanercept in the treatment of CP NB deserve attention.

Since marked elevation of CSF IL-6 is a hallmark of CP NB, treatment with tocilizumab, an anti-IL-6 receptor monoclonal antibody, is also considered to have beneficial effects. In fact, tocilizumab has been shown to be effective in a patient with refractory NB with high CSF IL-6 activities, who did not adequately respond to infliximab [41]. A clinical trial to confirm the efficacy of tocilizumab in the treatment of CP NB is therefore warranted.

8.6 Conclusion

Various neurological and neuropsychological manifestations are resulted from CVT or parenchymal involvement in BS. The latter is much more prevalent and called as NB, which consists of acute type and CP type. Diagnostic criteria for both types of NB have been now established. As for treatment, administration of corticosteroid should be considered depending on the severity of the attack in acute NB. Colchicine, low doses of steroids and various immunosuppressive drugs have been used anecdotally for prevention of the recurrence of attacks of acute NB. As to CP NB, one should realize that corticosteroids and cyclophosphamide are not effective at all. Low-dose MTX as well as infliximab has been shown to be effective for CP NB. In addition, tocilizumab appears to be promising.

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Ocular Involvement and Behçet Disease

9

Lorenzo Vannozzi, Ugo Menchini and Massimo Accorinti

9.1 Epidemiology

Ocular involvement in Behçet disease (BD) has been reported, as first manifestation or further complication, since the earliest descriptions of this dramatic and intriguing syndrome. On ocular signs and symptoms, although with associated systemic manifestations, scientists based over the centuries their different definitions of this polymorphic disease. BD was first described in the fifth century B.C. by Hippocrates of Kos (460–377 B.C.) in the 7th case of his third "Epidemion" book. He describes an illness whose manifestations fit very well with the cardinal signs of the later defined Adamantiades–Behçet disease: "…*But there were also other fevers*, *as it will be described. Many had their mouths affected with aphthous ulcerations. There were also many defluxions about the genital parts, and ulcerations, boils* (*phymata*), *externally and internally about the groins. Watery ophthalmies of chronic character, with pains; fungous excrescences of the eyelids, externally and internally*, *called fici*, *which destroyed the sight of many persons*…" [1]. Starting form ocular manifestations, in 1930 the Greek ophthalmologist Benediktos Adamantiades (1875–1962) reported a case of recurrent iritis with hypopyon, oral aphthosis, scrotal ulcers, thrombophlebitis, and bilateral sterile arthritis, which he hypothesized was due to bacterial or focal illness [2]. In 1937 the

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Turkish dermatologist Hulusi Behçet (1889–1948), published in Germany the association of oral aphthosis, genital ulcers, and recurrent uveitis with hypopyon in two patients [3], describing accurately during the following years signs and symptoms associated to the initial so-called triple symptoms complex [4]. In honor of his studies on the disease, in 1941 Jensen introduced the term "Behçet's syndrome" to describe the triad of oral aphthosis, genital ulcers, and uveitis associated with hemorrhagic colitis [5]. Thanks to the work of these authors and many others, the disease reached the definition and the classification criteria summarized and adopted in 1990 by the International Study Group, which considered the ocular involvement one of the most important feature of BD [6].

BD has been described all over the world, but its prevalence is certainly higher in the Mediterranean area (especially Turkey), in the Middle East, and in the Far East. This geographic area, spreading form the 30° to the 45° north latitudes in Asia and Europe, corresponds exactly to the highest distribution of the HLA-B51 antigen as well as to the old commercial route from the East to the West, leading Ohno to coin the term "Silk Route disease" [7]. However, people genetically originating from an endemic region who have emigrated to different nations appear to carry a significantly lower risk of developing BD, as it has been demonstrated among Japanese living in Hawaii or in the rest of United States [8] and among Turks living in Germany [9]. This finding suggests that environmental factors may also play an important role in the development of clinical manifestations.

9.2 Ocular Involvement in BD

Ocular involvement typically occurs within 2–4 years from the onset of BD, but it might also be the initial manifestation of the disease in approximately 10–20 % of cases [10, 11]. Among patients carrying the diagnosis of BD, the frequency of ocular involvement varies in series reported from dermatologist, rheumatologist, or clinicians, reaching higher prevalence (around 90 %), as expected, in data from eye centers [12–14]. Among children, the reported ocular involvement varies from 27 to 80 %, depending on the clinical setting [15–17].

The frequency of BD associated uveitis in tertiary uveitis centers all over the world varies considerably from less than 1 % to more than 30 %. This proportion seems to vary also over time, showing a diffuse decreasing incidence rate of BD and a shift toward milder forms of the disease; it has been suggested that improvement in the environment or health care may lead to a change in the BD course in populations with a stable genetic [18]. In summary, although BD is rare in general population, a large proportion of cases (perhaps one-half to two-third) suffer ocular involvement.

An international study on 1,465 patients from 25 eye centers in 14 countries, documented that the mean age of eye disease onset was 27.4 ± 10 years old [19]. The diagnosis of BD in childhood is unusual: an onset of the disease before the age of 16 years old is reported in 3–5.3 % of cases [15, 20, 21]. Concerning the anatomic location of uveitis, panuveitis decreases as age increases, while the proportion of

patients presenting with anterior uveitis correspondingly increases. Ocular involvement is usually bilateral across all ages [22]. Studies reported different incidence of manifestation of BD among sexes: females more frequently develop genital aphthosis and skin lesions, males ocular involvement, vascular involvement, and neurologic disease [23]. In the International Collaborative Study previously cited, 68.3 % of the patients were males and 31.7 % females, with an overall male-to-female ratio of 2.15:1 [19]. The same data showed also that panuveitis and a poor visual acuity were more common in men than in women, while bilaterality and recurrence of uveitis were similar between sexes [19].

The International Collaborative Study found the presence of HLAB51 in 62 % of the patients, with its maximum expression in Greece (81.9 %) and minimum (42.9 %) in the United Kingdom [19]. If the presence of HLA-B51 allele could represent a prognostic factor of ocular BD remains still unclear. A study analyzing Turkish patients found no correlation between HLA-B51 and the presence or the type of Behçet uveitis (BU), but showed a more recurrent ocular disease in the allele-positive subjects, representing possibly a negative factor for visual prognosis [24]. Differently, other authors reported a higher frequency of ocular manifestations in HLA-B51 patients although no association was found with the severity [25]. A recent study on Japanese Behçet patients reported HLA-A2601 allele as a negative factor for the development of ocular manifestations and their poor prognosis [26].

The most common ocular manifestation of BD is uveitis, although many different ocular lesions, such as keratoconjunctivitis, conjunctival ulcerations, keratitis, corneal neovascularization, episcleritis, scleritis, myositis, orbital inflammation, lacrimal gland involvement, isolated optic neuritis, and extraocular muscle palsies, have been described in this patient population. Behçet uveitis is usually bilateral in the large majority of the patients (63–100 %) [12, 19, 27–31]. Initial anterior unilateral manifestations might be seen, whereas recurrent attacks tend more commonly to bilaterally involve the posterior segment of the eye and the vitreous [11]. Isolated anterior uveitis seems to present in less than 12 % of BD patients in different series, while posterior uveitis or panuveitis represent the most common ocular manifestation of the disease [11–13, 19, 27, 28, 31–33].

A recent review offers a precise analysis of the epidemiological data available nowadays on ocular findings and complication of BD [34]. The main presentation of ocular BD is typically a sudden, non-granulomatous, and recurrent uveitis. It usually has a relapsing-remitting course, with spontaneous resolution. Ciliary injection is not a constant feature in eyes with ocular BD, and, if present, is typically milder than in other types of severe anterior uveitis. It is non-infrequent to observe a disproportion between a mild ciliary injection and the formation of hypopyon. The deposition of a "cold hypopyon" can be severe or very limited ("angle hypopyon") and it is described in 5–32 % of the patients; however its incidence may be higher than reported because of the its fast resolution that represent, along with its mobility, a peculiar characteristic [11–13, 19, 27, 28] (Fig. 9.1).

Retinal vasculitis is the most typical posterior segment involvement in BD (79–100 % of the cases) (Table 9.1), especially if searched by fluorescein angiography and in patients with an history of ocular BD lasting for more than 1 year.

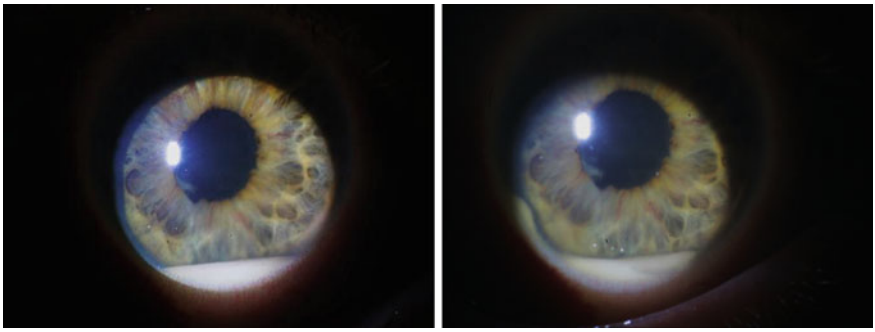

Fig. 1 Movable cold hypopyon in Behçet uveitis

It usually presents as a perivasculitis of the veins and, less commonly, of the arteries [11–13, 19, 27, 28, 32]. Foci of necrotizing retinitis have been described in 32–53 % of eyes: retinal infiltrates appear suddenly as yellow-whitish lesions, varying in number, dimension, and distribution. Usually, small superficial lesions disappear in several days without any visible scarring; larger and deeper retinal infiltrates can be more persistent and heal with scarring [12, 27–29]. Other common described signs of posterior ocular involvement are retinal hemorrhages, associated or not with occlusive retinal periphlebitis (21–27 %), and papillitis [12, 27, 28, 32, 33] (Table 9.1). Vitreous involvement is also frequent in BD, being present in 66–100 % of the patients [11–13, 19, 27, 28]. Vitreitis, an indicator of the inflammatory activity of BD, can completely obscure the view of fundus details at the onset of the uveitic attack. Remitting the inflammatory attack, the vitritis resolves in weeks, showing initially, in 30 % of the patient, the formation of strings of pearl-like precipitates on the surface of the inferior peripheral retina [10].

The development of macular edema, cataract, or increase in intraocular pressure often complicates the management of patients affected by BD. Macular edema is a frequent complication during the inflammatory attack of posterior uveitis; it can resolve with the initial treatments or can persist and became chronic leading to macular structural damage. Cataract development and the rise of intraocular pressure can be consequence of both the inflammatory disease and the systemic or local corticosteroids used for the treatment.

In severe cases, periphlebitis may lead to branch retinal vein occlusion, gliotic inflammatory vessel sheathing (permanent once established), iris deformity or atrophy, macular degeneration with pigment epithelial changes, scarring and epiretinal membrane formation, and retinal ischemia and retinal or optic atrophy. In some cases, neovascularization of the iris, retina, or optic disk develops, leading, if untreated, to intravitreal hemorrhage and tractional retinal detachment. Severe or inadequately treated eyes may develop phthisis bulbi and may require enucleation. Uncommon posterior segment complications of BD include branch retinal artery occlusion and macular hole. Repeated episodes of posterior segment inflammations and complications can result in end-stage ocular BD, defined as eyes with total optic atrophy, vascular attenuation and sheathing with occluded and

Table 9.1 Ocular findings reported in patients with Behçet uveitis in series from Brazil, Italy, Switzerland, Turkey, Tunisia, China, India, and Midwest United States (US)

%	Barra et al. [31]	Pivetti Petti et al. [32]	Ambresin et al. [33]	Tugal-Tutkun et al. [27]	Khairallah et al. [28]	Yang et al. [12]	Sachdev et al. [13]	Saleh et al. [29]
	Brazil	*Italy*	*Switzerland*	*Turkey*	*Tunisia*	*China*	*India*	*Midwest US*
	1991	*1993*	*2002*	*2004*	*2006*	*2008*	*2009*	*2012*
	$N = 49$	$N = 174$	$N = 35$	$N = 880$	$N = 62$	$N = 437$	$N = 49$	$N = 36$
Hypopyon	34.7	17.2	26	12	5.4	32.4	34.7	22
Vitritis	–	–	100	89	94	66.4	–	–
Retinal vasculitis	100	100	95	89	89	81.2	79	86
Retinitis	–	–	–	51	32	53.2	–	33
Retinal hemorrhages	–	–	–	26.9	26	21.4	–	–
Papillitis	–	–	100	5.5	64	67.3	–	–

Adapted from: Khairallah et al. [34]

sclerotic vessels, diffuse retinal atrophy with variable chorioretinal pigmentation and scarring. This scenario was not infrequent in the past [12, 13, 27–29, 31–33] (Table 9.2), while nowadays some different therapeutic options available to try to control the course of ocular BD seem to better preserve a useful visual acuity in long-term follow-up.

9.3 Treatment of Ocular Involvement

BD is a systemic condition and therefore the therapeutic approach has to consider both the single organ manifestations (i.e., the eye) as the other organ lesions. Nevertheless it is of note that ocular lesions, as well as neurologic ones, are usually the most severe, requiring a more aggressive and intense immunosuppressive treatment than normally is able to control all the other manifestations of the disease.

In 1970 Mamo has reported that 50 % of patients with BD treated with only steroids lose visual acuity from at least one eye within 2 years from ocular disease onset [35]. Therefore, it is obvious that almost every kind of immunosuppressive therapy has been used during time to try to lower the number of uveitis recurrence and to preserve visual acuity. Although corticosteroids are not sufficient to control the ocular manifestations of BD, their use is still useful in controlling the acute phase of inflammation waiting for immunosuppressive drugs to reach their therapeutic levels of efficacy. Nevertheless corticosteroids have almost no effect on the occurrence of long-term *sequelae*. Apart from the topical therapy, the systemic approach seems to be reasonable when uveitis is concomitant to other organ lesions, such as bipolar aphthosis, skin involvement, or arthralgia/arthritis. As already mentioned uveitis is usually a panuveitis with retinal vasculitis; anterior segment involvement can be successfully treated with topical steroids (prednisone 1 drop/hour or dexamethasone 6–8 drop/day) and mydriatic and cycloplegic eye drops (tropicamide 1 % 1 drop/qd, atropine 1 % 1 drop 2–3 times/day), and in case of a particularly severe involvement, peribulbar injections of depot steroids (triamcinolone 40 mg or methylprednisolone 40 mg) can be given every 15–60 days [36]. Useful systemic steroids for uveitis in BD have to reach a daily dose of 1 mg/kg of prednisone or equivalent or, alternatively, can be given intravenously (methylprednisolone 1 gr/day for three consecutive days) [37]. A very gradual tapering will follow after the inflammation has subsided, and sometimes, in order to maintain uveitis under control, a small daily dose of corticosteroids (i.e., prednisone <10 mg) can be given alone or in combination with immunosuppressive therapy. This therapeutic approach is also tried to reduce the total amount of immunosuppressive drugs and their related toxic effects. Nevertheless very few patients can be successfully treated by corticosteroids alone, especially those carrying risk factors that has been correlated with a bad ocular prognosis, such as male sex, young age at onset and neurological or systemic vascular involvement [14, 27, 32]. Therefore, there is an absolute indication in BD patients with uveitis

Table 9.2 Reported ocular complications in patients with Behçet uveitis in series from Brazil, Italy, Switzerland, Turkey, Tunisia, China, India, and Midwest United States (US)

%	Barra et al. [31]	Pivetti Petti et al. [32]	Ambresin et al. [33]	Tugal-Tutkun et al. [27]	Khairallah et al. [28]	Yang et al. [12]	Sachdev et al. [13]	Saleh et al. [29]
	Brazil	*Italy*	*Switzerland*	*Turkey*	*Tunisia*	*China*	*India*	*Midwest US*
	1991	*1993*	*2002*	*2004*	*2006*	*2008*	*2009*	*2012*
	$N = 49$	$N = 174$	$N = 35$	$N = 880$	$N = 62$	$N = 437$	$N = 49$	$N = 36$
Macular edema	12.2	–	68	44.5	19.8	38.2	59.3	36
Cataract	41.7	32.7	8.5	38.5	31.5	77.4	58.2	42
Persistent posterior sinechiae	–	–	2.8	26.1	32.4	23.9	–	–
Optic atrophy	18.8	42.5	12.8	23.6	13.5	16.2	27.5	11
Macular degeneration	–	–	–	19.4	–	3.9	–	8
Intraocular pressure rise	–	–	2.8	13.8	8.1	31.4	–	17
Epiretinal membrane	–	–	8.6	17	17.1	9.6	–	36

(continued)

Table 9.2 (continued)

%	Barra et al. [31]	Pivetti Petti et al. [32]	Ambresin et al. [33]	Tugal-Tutkun et al. [27]	Khairallah et al. [28]	Yang et al. [12]	Sachdev et al. [13]	Saleh et al. [29]
	Brazil	*Italy*	*Switzerland*	*Turkey*	*Tunisia*	*China*	*India*	*Midwest US*
	1991	*1993*	*2002*	*2004*	*2006*	*2008*	*2009*	*2012*
	$N = 49$	$N = 174$	$N = 35$	$N = 880$	$N = 62$	$N = 437$	$N = 49$	$N = 36$
End-stage disease	–	–	–	13	3.6	–	–	–
Branch retinal vein occlusion	–	–	–	6.6	8.1	31.3	–	6
Disk/retinal neovessels	–	8	–	4.3	5.4	7.2	–	8
Macular hole	–	–	1.4	2.6	–	1.9	–	–
Intravitreal hemorrhage	–	–	–	2.3	3.6	–	–	11
Phthisis bulbi	–	–	1.4	1.8	0.9	3.8	–	–
Retinal detachment	–	6.3	1.4	1.4	0.9	10.7	–	–

(continued)

Table 9.2 (continued)

%	Barra et al. [31]	Pivetti Petti et al. [32]	Ambresin et al. [33]	Tugal-Tutkun et al. [27]	Khairallah et al. [28]	Yang et al. [12]	Sachdev et al. [13]	Saleh et al. [29]
	Brazil	*Italy*	*Switzerland*	*Turkey*	*Tunisia*	*China*	*India*	*Midwest US*
	1991	*1993*	*2002*	*2004*	*2006*	*2008*	*2009*	*2012*
	$N = 49$	$N = 174$	$N = 35$	$N = 880$	$N = 62$	$N = 437$	$N = 49$	$N = 36$
Iris neovessels	–	–	2.8	1.2	6.3	2.2	–	–
Retinal tear	–	–	–	1.1	–	–	–	–
Neovascular glaucoma	–	–	–	0.9	2.7	1.7	–	–
Follow-up	–	Mean, 6.6 yy in 74.7 % of patients	Mean, 5.7 yy	>5 yy in 38 % of patients 1–5 yy in 32.4 % of patients	Mean, 68.9 months	Mean, 47 months	Mean, 4.9 yy	At least 12 months after immunosuppressive therapy
Final visual acuity (FVA)	20/400 or less in both eyes in 2.3 % of patients	–	0.79 ± 0.70	–	Less than 20/200 in 30.6 % of eyes	–	Less than 20/400 in 38 % of eyes	Improvement of FVA in 60 % and stability in 40 % of patients treated with biologic agents

Adapted from: Khairallah et al. [34]

affecting the posterior segment of the eye to immunosuppressive therapy [36]. It is mandatory for the patient, before being considered for such a therapy, to undergo a systemic evaluation of his/her clinical *status* as well as every useful laboratory and radiologic examination in order to check for subclinical disease and to appropriately monitoring the possible side-effects related to each individual therapy. Almost every immunosuppressive drug has been used in ocular BD, and most consistent data are available from antimetabolites (azathioprine), alkylating agents (chlorambucil and cyclophosphamide), calcineurin inhibitors (cyclosporine, tacrolimus), and biologic drugs (interferon, anti-TNF alpha agents).

Azathioprine. Is the only drug than has been proven to be effective in BD patients in a double-blind placebo-controlled trial in controlling intraocular inflammation, maintaining visual acuity, and preventing onset and/or progression of uveitis [38]. Nevertheless, azathioprine did not reach the same therapeutic goal if administered two or more years after uveitis onset [39]. The usual dose is 2–3 mg/kg/day and it might need 2–3 months before exerting any effect. In this time corticosteroids therapy should be maintained to prevent relapses. Most common side-effects are bone-marrow suppression, gastrointestinal discomfort (nausea, vomiting, diarrhea), hepatotoxicity, and rarely secondary infections [36, 40, 41]. Azathioprine has been indicated by EULAR recommendations as the first-line immunosuppressive drugs in the treatment of posterior segment involvement in BD [42], although the highest rate of long-term remission in BD uveitis has been obtained with the use of interferon [43], and infliximab has been proposed by some Authors as first-line therapy to induce remission, because of its very rapid action [44].

Chlorambucil. In 1970 Mamo has introduced chlorambucil for the treatment of BD patients with ocular lesions unresponsive to corticosteroids therapy [35]. Chlorambucil was therefore the first immunosuppressive drug ever used to treat patients with BD, especially those with ocular involvement. Different therapeutic strategies can be used with chlorambucil: the classic one is to administer the drug at an initial dose of 0.1 mg/kg, increasing gradually up to 0.2 mg/kg [36, 40, 41, 45]. The second option is to start with 2 mg/day and to keep on increasing the dosage by 2 mg/day each week until a clear immunosuppression has been achieved (white blood cells count = 2,400 or platelet 100,000) or unless there is a clinical remission; if these blood count parameters are reached, chlorambucil therapy is abruptly terminated [46]. Although chlorambucil is a slow-acting drug, reaching its maximal effects after 2–3 months of therapy, with both this regimen it is possible to obtain a sustained remission of the disease [14, 45–47]. Pivetti-Petti has demonstrated that an early chlorambucil therapy is able to maintain a visual acuity greater than 8/10 in 70 % of the eyes after a follow-up of 10 years, while patients treated initially with corticosteroids and late with chlorambucil retained a visual acuity of 8/10 or higher in 19 % of the eyes only [45]. Nevertheless in a cohort of patients from Saudi Arabia no such results have been obtained, with 75 % of the eyes treated with chlorambucil as monotherapy having a visual acuity of 20/200 or less [48]. Chlorambucil carries numerous side-effects, mainly myelosuppression, which usually is moderate, gradual, and reversible [49], but

might be abrupt and profound, persisting for months after stopping therapy. Gonadal dysfunction is the second most important side-effects. This produces irreversible azoospermia in men and ovarian dysfunction in women and therefore sperm banking and ovum cryopreservation should be offered before therapy starting. No increase of overall mortality has been found in patients receiving alkylating agents for uveitis, although a non-significant increase in cancer-related mortality was observed [50].

Cyclophosphamide. It was the second immunosuppressive drug used with favorable results in controlling uveitis and preventing ocular relapses in BD patients [51] and even administered orally it has shown successful results in patients previously unresponsive to corticosteroids [52]. It can be given either intravenously (750–1,000 mg/square meter every 4 weeks) or orally (1–2 mg/kg/day) [36, 40, 41], providing a good hydration of the patient to avoid or reduce the most common side-effect, the hemorrhagic cystitis. Other even more dangerous side-effects are bone-marrow depression and gonadal dysfunction, but the latter is less frequently encountered in comparison with chlorambucil (60 % of the cases will develop azoospermia and amenorrhea) [36, 41]. Less common adverse effects are hepatotoxicity and alopecia, while there might be a possible increased risk of cancer mortality [50]. Cyclophosphamide has been compared to cyclosporine for the treatment of BD patients with controversial results: some studies have demonstrated its superiority in the treatment of BD patients [14], while Ozyazgan and coll have reported in a single masked trial done in Turkey more favorable results with the administration of cyclosporine, especially in the first 6 months of therapy [53].

Cyclosporine-A. It was for a long period the most widely used drugs to treat ocular lesions in BD patients. Many studies have demonstrated its efficacy, alone or in combination with low-dose steroids, both to treat acute attacks and to reduce uveitis relapses [54–57]. It is administered at 3–5 mg/kg/day, because higher doses have exerted a significant nephrotoxicity [36, 40, 41], and it has a more rapid action than other classic immunosuppressive drugs [58]. Its therapeutic goal is reached more easily if cyclosporine is administered in combination with corticosteroids [59], although some studies have demonstrated its inferiority toward cytotoxic agents in controlling the most severe form of ocular lesions in BD patients [60, 61]. It carries numerous side-effects, most of them reversible and/or easily manageable with dose adjusting. Among them there are nephrotoxicity, manifested clinically as increase in serum creatinine and decrease in creatinine clearance, increase in blood pressure, hepatotoxicity (increase in serum transaminases and bilirubin levels), gastrointestinal discomfort (nausea and vomiting), hirsutism, and gingival hyperplasia [36, 40, 41]. It is of note that cyclosporine may also produce neurologic symptoms, including paresthesias, fine tremors, and myopathy as well as hallucinations, and a more complex neurotoxicity, difficult to distinguish form the neurologic lesions in BD [62, 63]. Considering that patients with BD and ocular lesions may develop a subclinical neurologic involvement demonstrated by NMR of the brain and multimodal evoked potentials [64, 65], it might be worthwhile, before giving this drug to the patient, to investigate their neurologic status. Our personal experience in the treatment of BD with ocular

involvement in 64 patients ever treated before with immunosuppressive drugs has demonstrated that although this drug is able to maintain or improve visual acuity from baseline in 82 % of the eye, only 12 % of the patients were able to stop therapy and to obtain a sustained remission (mean follow-up after cyclosporine withdrawal: 53 months), while additional 30 % of the patients required prolonged therapy with either cyclosporine alone (9.4 %) or cyclosporine and low-dose steroids (20.3 %) [66].

Interferon alpha. It was the first "biologic" drug used extensively in patients with BD. Its way of action in this patient population is unknown, although a speculative hypothesis is based on its immunomodulatory action and/or on its antiviral performance. The doses used vary among the different population. Most of the Authors have treated BD patients with 3 million/unit 3 times/week subcutaneously of interferon alpha 2a with good results [67, 68], while in Germany a more aggressive therapy is administered [69]. The patients are given 6 million unit/day for 7 days stopping all the other drugs, especially corticosteroids. After the first week of therapy the dosage can be increased to 9 million/day in case of no response, leaved unchanged if a partial response has been obtained or decreased to 3 million/day in case of positive results. After the induction period that might last for up to 42 days, following a peculiar algorithm, the dosages are gradually tapered (4.5, 3 million/day, 3 million every other day, 3 million 3 times/week). After 6 months on 3 millions 3 times/week, in case of no ocular relapse, the therapy can be stopped [69]. With such an approach Deuter and coll have reported a 98 % of response to interferon therapy, with visual acuity unchanged or improved in 95 % of the eyes and no ocular relapses in 50 % of the patients after almost 4 years from therapy cessation [43]. Comparable results have been reported with different regimens: 87.5 % of responders and 87.5 % of visual acuity unchanged or improved in French patients treated with 3 M/U3 times/week (32 % of relapses after discontinuation) [68]; 71 % of remission after one year and 28 % out of relapses after a mean of 28 months from therapy cessation in Turkish patients treated with 4.5 M/U3 times a week for 3 months, then dose adjustment upon response [70] or with a dose-escalating algorithm from 3 M/U 3 times/week to 9 M/U 3 times/week in case of no efficacy for 24 months (95 % of the patients went to remission, 77 % out of relapses 12 months after discontinuation) [71]. Common side-effects includes flu-like symptoms (headache, fever, myalgia, arthralgia, fatigue), almost unavoidable when the dose is higher that 3 M/U, leukopenia and alopecia. Flu-like syndrome can be antagonized with simultaneous administration of 500–1,000 mg of paracetamol, and although it has to be considered a good prognostic factor, indicating the absence of anti-interferon antibodies, it is poorly accepted and tolerated by the patient [14]. Another important side-effect, differently reported in all the series, is the onset of depression with or without suicidal ideation [72]. In our experience 25 % of 12 patients developed severe depression, complicated in two cases by suicidal ideation, although the interferon dose did not exceed 9 M/U/week in three divided doses. Less common side-effects, are gastrointestinal changes, including diarrhea, dyspepsia, loss of appetite and weight loss, interferon-related retinopathy, cardiac lesions (cardiomyopathy), and

the occurrence of autoimmune thyroid disease, although thyroid autoantibodies presence is not infrequent in patients assuming interferon.

Anti-TNF alpha drugs. Tumor necrosis factors (TNF) inhibitors are the newest therapy for BD. TNF-alpha is a pro-inflammatory cytokine that has been found in uveitis and in BD patients in higher levels than controls both in serum and in aqueous humor [73, 74]. Moreover serum TNF-alpha levels correlates with recurrent uveitis. TNF-blocking agents comprise different drugs, but the most used in patients with BD are infliximab and adalimumab. Infliximab, a chimeric monoclonal antibody, is administered intravenously and the most used dosage is 5 mg/kg at initial dose, followed by the same dose at week 2, 6 and thereafter every 8 weeks. Adalimumab is a purely human monoclonal antibody; it is administered subcutaneously at 40 mg per dose at biweekly intervals. Side-effects can be either related to the way of infusion and to class of drugs. The clinical manifestation can range from local skin reactions at the injection site, pyrexia, and an influenza-like syndrome, to acute anaphylaxis and systemic inflammatory response syndrome, which could be fatal [75–77]. Other types of adverse events have been reported with the use of TNF-blocking agents, including onset of infections (upper respiratory and urine apparatus, opportunistic infections, and reactivation of latent tuberculosis), formation of anti-nuclear antibodies and antibodies to double-stranded DNA and lupus-like syndrome [78], central nervous system lesions (multiple sclerosis, Guillain-Barrè syndrome, chronic immune demyelinating polyneuropathy, multifocal motor neuropathy, progressive multifocal leukoencephalopathy) [79], new onset of uveitis (not in BD patients), cardiac adverse events (congestive heart failure, coronary heart disease or angina, arrhythmia, malignant hypertension and thromboembolic events) [77, 80], and malignancy. Most of the data concerning the risk of malignancy in anti-TNF-alpha users are drawn from studies on rheumatic diseases rather than uveitis, because of the largest number of patients with rheumatic diseases treated with such a drug. Data are not homogenous. Kempen et al. in a critical review have concluded that although there is an increased risk of cancer within 6 months of initiating TNF-inhibitor treatment, the absence of any observed effect on cancer risk in numerous studies with several years of follow-up suggest that TNF-inhibitors may allow pre-existing cancers to progress faster, but probably not induce cancer [50]. Another important issue in the use of TNF-blocking agents is the production of anti-drug antibodies. In this view point adalimumab therapy seems to be less immunogenic than infliximab [81]. It should be noted again that most of the information on TNF-blocking agents' adverse events are drawn by extensive series of patient with rheumatic disease and not with uveitis, because the former class comprises a significantly higher number of subjects.

Sfikakis was the first to publish the results on infliximab in treating 5 patients with Behçet's with one single infusion. He has obtained a remission of ocular inflammation in 24 h, and complete suppression 7 days after [44]. After the first description, many other case series have been published on the use of infliximab in the treatment of ocular manifestations in BD [82–86]. Particularly Ohno and coll [82] demonstrated that infliximab in patients with ocular refractory BD is able to

suppress the frequency of ocular attacks, and multiple administrations were well tolerated, although side-effects are not uncommon. Tugal-Tutkun showed that patients with BD resistant to a combination of corticosteroids, azathioprine, and cyclosporine can benefit from infliximab, which is effective in suppressing the occurrence of uveitis attacks, has a corticosteroid-sparing effect, and has favorable implications for the visual prognosis of this patient population [83]. We have observed a significant reduction in the number of ocular relapses, in the mean daily dose of corticosteroids and in extraocular manifestations of BD in 12 Italian patients with BD treated with infliximab and followed for a median period of 15 months, although it is of note that 33 % of them developed infections during the treatment period [84]. Okada et al. [86] have demonstrated that infliximab is effective in the treatment of 69 % of uveitis associated with Behçet's while 23 % of the patients showed a partial response. No patient worsened, and 44 % were free of attacks during therapy, with non-serious adverse effects occurring in about half of the patients. Infliximab seems to be also effective in the treatment of retinal neovascularization, one of the most serious complications of BD [87].

In a review of the literature on the use of biologics in Behçet's disease patients (325 patients treated with infliximab, 37 with etanercept and 28 with adalimumab), all inadequately controlled with or intolerant to other immunosuppressive regimens, 89 % of the patients with ocular involvement showed a positive clinical response and combination of infliximab with azathioprine and/or cyclosporine-A appeared superior to monotherapy for sustained ocular remission [85]. Also adalimumab has been shown effective in the treatment of uveitis in BD, with 90 % of complete resolution of uveitis at 4 weeks in 11 patients [88, 89].

Intravitreal route can be an alternative way to give anti-TNF agents avoiding systemic side-effects, although it does not exert any efficacy on systemic manifestation of BD. Farvardin [90] and Markomichelakis [91] have proven infliximab efficacy both in non-infectious uveitis and in BD's uveitis, with virtually no systemic or ocular side-effects. Nevertheless the efficacy of intravitreal infliximab seems to vanish overtime, with inflammation gradually increasing and visual acuity deteriorating 3 months after the injection; at 6 months virtually no changes from pre-injection conditions was found [92].

Anti-TNF alpha drugs can lose efficacy during time. In a review on 1,093 patients treated with such drugs, 254 with BD, adalimumab has the lower discontinuation rate (0.018 discontinuations/per patient included/per year of follow-up) compared to infliximab (0.058) and etanercept (0.16) [93].

In case of efficacy loss over time, studies on patients affected by rheumatic diseases have demonstrated that switching to a second TNF-alpha inhibitor is clinically relevant and the response to a second TNF-alpha inhibitor appears to be slightly better if the first TNF-alpha inhibitor was discontinued because of adverse events [94]. Therefore the switching from one TNF-blocking agent to another seems to be, even for uveitis and BD patients, another useful therapeutic option.

Two great problems can be encountered in the therapeutic management of BD patients with ocular involvement. The first is to choose the less toxic drug for each individual patient that theoretically will provide the best effect, taking in great

consideration risk factors (young age, male sex) and systemic conditions (neurologic and vascular lesions) [27, 32]. We are for sure more confident in giving a "classic" immunosuppressive drug to a female patient who has presented her first, predominantly anterior uveitis, in older age, while we prefer to treat as soon as possible a young male patient with a posterior involvement with either interferon or anti-TNF alpha. No doubt exists on the fact that long-term remission has been achieved in patients treated with alkylating agents [14, 45, 46] and more recently with interferon [42], while the new biologic drugs have not sufficient follow-up to demonstrate such an effect.

The second problem is how to withdrawn from therapy. There are no rules for how long a patient need to be treated, but the clinical experience seems to indicate a period ranging from 8 to 10 years during which uveitis relapses are more common [95]. Subsequently, either drug-induced or spontaneously, a period of long-term remission might appear. On the other hand, all the drugs used in BD patients might exert very toxic effects and, therefore, their use should be limited. Generally speaking, once an immunosuppressive drug is introduced to treat uveitis, the patient is usually taking systemic steroids and, many times, other immunosuppressive drugs also. The aim of the immunosuppressive drug is to reduce (hopefully eliminate) the systemic steroids. Once this goal has been obtained the patient is usually leaved on immunosuppressive therapy for at least 12 months. After this period, if no ocular neither systemic recurrence of the disease has been observed, a gradual withdrawal from the immunosuppressive drugs can be tried, and finally all the drugs should be stopped.

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Articular and Muscular Manifestations in Behçet's Disease

10

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Behçet's disease (BD) is a chronic, relapsing type of vasculitis of unknown etiology characterized by urogenital ulcers and ocular inflammation with cutaneous, musculoskeletal, vascular, and nervous system manifestations [1]. BD is included in the wide spectrum of vasculitis. Vasculitis is the principal pathologic finding in BD, and vessels of all sizes are involved, both in the venous and arterial systems. The etiopathogenesis of the disease remains obscure, although genetic predisposition, environmental factors, and immunological abnormalities have been implicated. People from the Far East, the Middle East, and the Mediterranean basin are more commonly affected than those from other parts of the world. In Northern Europe, central Africa, and the United States the disease is infrequent. All ages may be affected, although the frequency is higher in persons in the third or fourth decade. The sex predominance varies widely among the diseased population in different geographic areas [2–4]. Earlier studies suggested a male predominance in high prevalence areas, but more recent surveys indicate equal involvement of

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the sexes. In western countries, females predominate. BD may affect all organs and up to half of the patients with BD display rheumatic manifestations. However, muscular involvement in BD is rarely described in the literature.

10.1 Joint Involvement and BD

Articular manifestations are frequent in BD since articulations are involved in 40–71 % of BD patients according to different studies. Main clinical features of joint involvement in BD are described in Table 10.1 [5–9]. Joint involvement is the first manifestation of BD in 11–34 % and may appear several years before other symptoms. Knees, wrists, ankles, and elbows are more often affected while the involvement of the small joints of hands and feet is less common.

Arthralgia is the main symptom, found in up to 80 % of patients [5]. Arthritis is less common (7 %) and includes mono-articular and oligo-articular lesions. Erosive changes are rare including hand, foot, wrist, and knee [7]. They usually run an acute and recurrent course (76 %). Chronic course is less frequent [5].

Articular manifestations are significantly associated with cutaneous lesions (erythema nodosum) while vascular complications are less common in BD patients with joint involvement. Gur et al. have reported that BD patients with articular involvement were more frequently females, had more often erythema nodosum and had more human leukocyte antigen B51 positivity. In contrast, Ben Taarit et al. have reported a higher prevalence of joint manifestations in male patients [8].

Inflammation is sometimes found as increased erythrocyte sedimentation rate (ESR) and C reactive protein (CRP) level. Analysis of articular fluid usually reveals increase of polymorphonuclear neutrophil cells. Authors have reported non-specific inflammation in synovial biopsies [10–13]. Recently, Canete et al. analyzed synovial biopsies of nine BD patients and compared the findings to biopsies of 8 patients with psoriasis (PsA) arthritis in order to improve the understanding of mechanisms of articular manifestations in BD [14]. None of these

Table 10.1 Literature review of large studies on articular involvement in BD

	Frikha $n = 553$	Ben Taarit $n = 309$	Benamour $n = 601$	Ait Badi $n = 176$	Gurn = 63
Articular involvement	71. %	68.3 %	56.7 %	45 %	41.3 %
First symptoms		34 %	18 %	16.5 %	
Erosive form	1.4 %	0.6 %	2.3 %		
Arthritis		45 %	28 %	19 %	65 %
Sacroiliitis/SP		6/0.6 %	ND/1.4 %	7.5 %/5 %	38 %/ND
Site of joint manifestation		Knee, wrist	Knee, wrist		Knee, wrist
Association		EN			EN

SP, spondylitis; *EN*, erythema nodosum

patients received any immunosuppressive agents or corticosteroids before the analysis. The global degree of synovial inflammation was similar in the two types of arthritis. The analysis of the innate immune cell infiltration showed a striking neutrophilic inflammation in BD synovitis, whereas PsA displayed significantly higher numbers of mast cells. It was also not related to a difference in levels of CXCL8, a major chemokine involved in the recruitment of polymorphonuclear neutrophils (PMN). This neutrophilic inflammation in BD compared to PsA likely reflects a key feature in BD as previous studies have shown that the number of infiltrating PMN was already high in PsA compared with rheumatoid arthritis synovial tissue. In Yurdakul 's cohort, synovial biopsy in 12 patients also revealed paucity of plasma cells and in five cases lymphoid follicle formation [13]. Another previous study has also shown PMN infiltration in synovial tissues in BD [12] while others have reported that histopathological characteristics of synovial tissue in BD may also include lymphocyte and plasma cells infiltration [11]. Canete's study has shown that CD3+ T cells, but neither CD20+ B cells nor CD138+ plasma cells, were significantly increased in BD as compared to PsA. Further analysis of the T-lymphocyte population showed no clear shift in CD4/CD8 ratio or Th1/Th2/Th17 profile. There was also no significant difference in the number of cytotoxic cells (defined by CD8+ , CD56+ , perforin+ , or granzyme B+ cells), in BD compared to PsA synovitis. However, the levels of perforin released in the synovial fluid were five fold increased in BD compared to PsA, underscoring the key role of cytotoxicity in BD synovitis [14].

10.2 Uncommon Articular Features

Arthritis associated with BD is usually benign and non-deforming. Erosive arthritis is less common, involving 0.6–3.2 % of BD patients. Moreover, some studies suggest that hand involvement is probably underestimated in BD. Several studies have reported BD patients with erosive and deforming polyarthritis affecting small joints of hands and of wrists [7, 15, 16]. In Yurtkuran's study, 32 patients (56.1 %) had clinical hand findings [17]. Terminal phalangeal pulp atrophy was observed in 17 patients with BD (29.8 %), 16 patients (28.1 %) had rheumatoid-like hand findings like swelling of the proximal interphalangeal joint (PIP), erosions and swelling of wrists and ulnar deviation. Dorsal interosseous muscle atrophy was present in 12 patients (20 %) and 12 patients had erythema over the digits (20 %). Hand involvement seems to be more frequent in female patients. The difficulty is to know if these findings are related with BD or rheumatoid arthritis associated with BD. Some authors suggest that asymmetric erosive arthritis, negativity of rheumatoid factor and anti-CCP antibodies strongly suggest that these clinical findings are specific of BD. Very rare findings have also been reported such as bone erosion of sterno-costal joint [7, 16, 18]. Hip involvement is an uncommon event except in patients with bone necrosis associated to corticotherapy.

Axial involvement is also noted with inflammatory back pain in up to 29 % and sacroiliitis in 5–38 %, according to studies (Table 10.1). A defined spondyloarthropathy associated to HLA B27 is associated with BD in 0.6–5 %. Findings of investigations regarding the prevalence of enthesopathy in BD are inconsistent. Thus, it is difficult to assert a significant association between BD and HLA B27 spondyloarthropathy because there have been conflicting results for the prevalence of HLA B27, enthesitis, and sacroiliitis in patients with BD [19]. Popliteal cysts are possible and cysts breaking can mimic venous thrombosis [15].

10.3 Treatments

In most patients with BD, arthritis can be managed with colchicine. Two randomized controlled trials (RCTs) have tested the efficacy of colchicine in BD patients with arthritis and both showed beneficial effects [20, 21]. Colchicine 1–2 mg/day is indicated in recurrent joint manifestations, decreasing articular relapses.

One RCT with benzathine penicillin and open studies with indomethacin and oxaprozin showed some efficacy whereas azapropazone 900 mg/day and intramuscular depot corticosteroid was not effective. Anti-inflammatory drugs were efficient in articular manifestations in 86 % of patients of Ait Badi's cohort [5]. Corticosteroids are used (5–10 mg per day) in articular involvements resistant to anti-inflammatory drugs. Some authors have reported efficiency of corticosteroids and methotrexate in patients with hand involvement [16].

In EULAR recommendations, experts recommend that IFNα, azathioprine, and TNFα blockers may be tried in rare cases with resistant, long lasting, and disabling attacks [22].

In Arida's review [23], of the 53 patients who received infliximab, improvement of articular involvement was evident in 94 %. Of patients with arthritis, who participated in prospective studies evaluating the effect of repetitive infliximab injections, a sustained response was evident in 91 %. For these patients, it appears that combination therapy with methotrexate and/or cyclosporine-A was equally effective to infliximab monotherapy. Of the 6 and 5 patients who respectively received etanercept and adalimumab, improvement of articular involvement was evident in 100 and 60 %, respectively.

10.4 Muscle Involvement in BD

Muscle involvement is uncommon in BD. There are only few cases disclosing muscular involvement in BD. Worthman et al. reported a BD patient with a fluctuating acute necrotizing leukocytoclastic myositis suggesting the hypothesis of neutrophil-mediated vasculitis and myositis in BD [24]. Actually, light microscopic examination revealed a prominently granulocytic-monocytic infiltration of the muscle with severe necrosis. Vascular deposition of immune complexes was

detected by direct immunofluorescence. Electron microscopy revealed severe structural damage and phagocytosis of muscle fibers. An infectious (bacterial, viral, fungal, or parasitic) etiology could be excluded by specific staining techniques and by immunohistochemistry. The relevant literature on muscular involvement in BD was also reviewed by Worthman et al. Among 12 patients with myositis, 10 were of male gender. This review showed a predominance over the lower extremities with muscular symptoms like pain and swelling. Myocarditis was found in one case [25]. In five cases, myalgias were found without the previous diagnosis of BD. It was suggested that two different stages of inflammation occur in BD. In the acute stage, it presents as a granulocytic-monocytic necrotizing reaction developing from a neutrophil-mediated vasculitis. In the later phase, lymphocytic infiltrations predominate. Another case report showed a biopsy of the right gastrocnemius muscle demonstrating a segmental necrotizing vasculitis, predominantly affecting small perimysial arteries [26]. Arterial walls and perivascular areas were infiltrated by lymphocytes and macrophages. The lymphocytic infiltrate consisted predominantly (80 %) of CD3-positive T cells, which were made up of CD4-positive (80 %) and CD8-positive (20 %) cells. CD79a-positive B cells were intermingled to a minor degree.

Jo et al. reported a case who exhibited multiple nodular, patchy, or diffuse intermediate signal intensity areas on the T1-weighted image, and a high-signal-intensity on the T2-weighted image in the bilateral muscles of the lower leg, which are typical for MRI findings in muscular involvement of BD [27]. They also found a fascial enhancement and T2 high-signal-intensity edema of the subcutaneous fat layer.

The differential diagnosis of BD is based on imaging findings and includes infectious myositis, with or without fasciitis; compartment syndrome; and traumatic muscle injury [28]. Distinguishing BD from infectious myositis can be difficult but is critical because immunosuppressive therapy is contraindicated in the treatment of infection. Moreover, some authors have reported myonecrosis in BD that can mimic soft tissue abscess. Therefore, awareness of this entity in the appropriate clinical setting is important for initiation of appropriate and timely treatment. Multiplicity and bilaterality can help insure the correct diagnosis of muscular involvement of BD when it occurs in patients with a history of BD. Clinically, muscular involvement of BD presents with milder symptoms than does an infection. Furthermore, muscular involvement of BD yields negative culture results [27].

The prognosis of BD is typically favorable, with frequent spontaneous resolution. Anti-inflammatory drugs, corticosteroids, and immunosuppressants are administered in the more severely affected cases.

10.5 Muscular Manifestations and Treatment

Muscle manifestations can be observed after treatment by colchicine. Several reports have described myopathy and rhabdomyolysis induced by colchicine [29, 30]. Commonly, proximal weakness is the hallmark symptom when the diagnosis of

colchicine-induced myopathy is made. Frequently, muscular complications are observed under high doses of colchicine. Several risk factors are noted, such as chronic renal failure, hepatic failure, drug interaction (CYP3A4 inhibitors), and alcohol [30]. Most patients who have myopathy associated to colchicine have good recovery after withdrawal of colchicine and related medications.

10.6 Conclusion

Articular involvement is very common in BD including, mainly, inflammatory arthralgias affecting more frequently knees, wrists, and elbows. Arthritis is also described but is far less common and can involve small joints of hands. In several studies, synovial analysis show polymorphonuclear neutrophil cells in BD. Muscular manifestations are not common and affect mainly muscles of lower extremities. Histological findings of muscle biopsies suggest neutrophil-mediated vasculitis. Moreover, muscle complications can be linked to BD treatment such as colchicine.

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11 Cardiovascular Issues: Aneurysms and Pseudoaneurysms, Thrombosis, Atherosclerosis, and Cardiac Involvement

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Behçet syndrome (BS) is a multisystem disease characterized by a diverse spectrum of clinical manifestations including cardiovascular involvement. These important and serious manifestations occur in 7–46 % of patients, with lethal outcome in about 20 % of severe cases [1]. BS is a distinctive perivasculitis that may involve both veins and arteries of all sizes, ranging from great blood vessels to capillaries. The major manifestations are venous and arterial thrombosis and arterial aneurysms, but venous involvement is typically more evident. Arterial occlusions and aneurysms sometimes coexist, [2] as well as arterial lesions and venous thrombosis that may affect the same patients [3, 4]. After a first event, other vascular lesions tend to occur. In 2006, vascular lesions were added to the international criteria for Behçet's disease (ICBD) and the term "vasculo-Behçet" is currently adopted for conditions where large vascular lesions are the main feature. Less frequently, heart involvement occurs in BS patients, intracardiac thrombosis being the most frequent, followed by pericarditis, myocarditis, coronary, and valvular disease [5].

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11.1 Aneurysms and Pseudoaneurysms

Arterial involvement makes up 25 % of all vascular complications of BS [6]. Aneurysms and pseudoaneurysms are the main arterial manifestations [7] involving both aortic and peripheral arteries. They are the leading cause of death because of risk of rupture and consequent bleeding [8]. Aneurysms are usually multiple and widespread, fusiform or saccular and sometimes a thrombus is found on their wall [9]. Aneurysm-related problems affect 60 % of all arterial complications, whereas arterial occlusions and stenosis are less common and have a better outcome [10].

The underlying pathological, basic lesion is a necrotizing arteritis. An intense inflammatory infiltration by neutrophils, lymphocytes, and plasma cells with several histiocytes and eosinophils, involves the media and the adventitia, causing destruction and loss of media elastic and muscle fibers with the proliferation of vasa vasorum along with their occlusion, eventually leading to fibrosis [11]. The inflammatory obliteration of vasa vasorum and consequent transmural necrosis may cause the formation of a pseudoaneurysm or the rupture of the arterial wall [12] whereas occlusions and stenosis mostly affect the medium and smaller arterial vessels in which vasa vasorum alterations are less critical [9].

Abdominal aorta is the most common site of aneurysms formation. Other common sites are pulmonary arteries, carotid, femoral, and popliteal arteries [11]. They may also occur anywhere in the circulation system. Aneurysms and pseudoaneurysms in unusual locations such as ulnar, celiac, subclavian, left anterior descending, tibio-peroneal, iliac, and superior mesenteric arteries have also been reported in BS patients [13, 14]. Coronary artery aneurysms occur in 1.5–5.0 % of patients [15] and may be isolated or associated with coronary stenosis. In some cases they are asymptomatic but sometimes may result in myocardial infarction [16]. Valsalva sinus aneurysms are also described as isolated complications or combined with coronary artery or other sinus aneurysms [17]. Aorta rupture or aortic valve regurgitation are the most common reported complications [18]. Less common sites of BS aneurysms are intracranial, affecting mostly middle cerebral artery [12], and thorax [19, 20].

A serious clinical problem is related to the involvement of pulmonary arterial circulation where both aneurysms (pulmonary artery aneurysms, PAAs) and occlusions may occur. PAAs affect 1–10 % of BS patients and are the most important cause of mortality and morbidity in BS. PAAs may coexist along with venous thrombosis of the lower limbs in Hughes-Stovin syndrome (HSS), probably a variant of BS. Other vascular complications reported to be associated to PAAs are caval vein thrombosis, peripheral aneurysms, and intracardiac thrombosis [21, 22]. Parenchymal lung manifestations, such as nodules and cavities, may be present usually in patients who have also active disease outside the lungs and systemic symptoms [23]. The involvement is usually multiple and bilateral, affects the main pulmonary arteries and their lobar branches and sometimes aneurysms filled with thrombi may be found [24].

A careful screening for aneurysms should be performed in BS patients because it is a life-threatening condition. It is important to look for signs or symptoms suggesting these vascular complications, although aneurysms are often asymptomatic. Abdominal pain, constipation, pulsating masses, retroperitoneal hematoma, and hemoperitoneum may be manifestations of abdominal aortic aneurysms. The presence of chest pain, dyspnoea, hemoptysis, are the most common symptoms of PAAs complications whereas subarachnoid hemorrhage may be the manifestation of intracranial aneurysm rupture. Contrast-enhanced tomography or magnetic resonance imaging is recommended for initial assessment and follow-up of aneurysms in these patients [25]; angiography is a valid diagnostic method, but there is a high risk of pseudoaneurysm formation at the site of catheter insertion. Actually, not only spontaneous aneurysms occur frequently in BS but also pseudoaneurysms are caused by vascular injuries. Surgical treatments or any vascular diagnostic procedures might lead to vascular disease reactivation through formation of false aneurysms, reflecting a pathergy-like effect in the vessels wall [26]. Invasive approaches should not be applied in the acute phase of the disease, but should be considered only during remission periods. Immunosuppressive therapy is recommended to induce remission in arterial vascular disease, so preventing also recurrences and postoperative complications [27, 28]. If necessary, surgery should be performed only after immunosuppressive therapy. Artery bypass represents the first line surgical procedures for arterial occlusions [29], artery ligation is used to treat peripheral aneurysms, and graft insertion is the conventional surgical management of abdominal aortic aneurysms [11], whereas endovascular approach, a minimally invasive technique to repair abdominal aortic aneurysms, has been growing over the past years [30]. Immunosuppressive treatment is also the first line therapy for pulmonary aneurysms. The European League Against Rheumatism (EULAR) suggests pulses of cyclophosphamide and high dose of corticosteroids [31] for at least 2 years, followed by azathioprine. Surgical treatment is often not successful because aneurysms are usually multiple, and endovascular embolization should be used in emergencies [32] or in resistant cases. Finally, cases of patients with PAAs successfully treated with anti tumor necrosis factor-alpha (TNF-α) monoclonal antibodies have been recently reported [33, 34]. This therapeutic option should be considered in patients who do not respond to standard immunosuppressive treatment.

11.2 Thrombosis

The prevalence of thrombosis in BS ranges from 14 to 39 %, according to different studies [35]. Venous thrombosis is the major clinical vascular involvement in BS. It makes up 75 % of all vascular complications [26] and deep vein thrombosis (DVT) of lower extremities is the most common manifestation and the first vascular episode in 78 % of patients [6]. Venous thrombosis occurs more frequently in males and in patients with active disease during the early years [36, 37], and

tends to recur. Systemic symptoms such as fever and fatigue and high blood levels of acute phase proteins are very common in BS patients with venous thrombosis [38].

Arterial occlusions are infrequent in BS. They are mostly associated with aneurysms such as in pulmonary artery involvement, where thrombosis in situ of the main pulmonary arteries is strongly associated with PAAs, or in coronary arteries in which occlusions and aneurysms may coexist. Arteritis, rather than atherosclerosis, is the main feature of arterial lesions. They may be asymptomatic or cause ischemic symptoms, depending on the development of collateral circulation. Intermittent claudication or gangrene of the lower limbs may be the clinical manifestations of peripheral arterial stenosis or occlusions. Mesenteric artery occlusions leading to intestinal infarction have also been reported [39], whereas coronary or cerebral arteries occlusions, resulting in acute myocardial infarction or stroke, are not frequent.

The details of pathogenetic mechanisms underlying thrombogenesis in BS are poorly known. Systemic inflammation and vasculitis seem to be the most important factors, promoting a pro-thrombotic condition and leading to the formation of a thrombus tightly adherent to the vessel wall [40] with a low rate of embolism [41, 42], especially during active disease. Thus, inflammation and not coagulation abnormalities is the main trigger of thrombosis in BS. A close relationship exists between inflammation and hemostasis; BS may be a model of inflammation-related thrombosis [43]. Different mechanisms by which inflammation is able to affect endothelial factors, coagulation, and fibrinolytic systems could contribute to thrombosis in BS [44, 45]. Several hemostatic factors have been investigated in BS with various results. High levels of pro-coagulant endothelial agents, such as circulating von Willebrand Factor (vWF) and vascular endothelial growth factor (VEGF) were found mainly in patients with active disease and high levels of tissue plasminogen activator (t-PA) were observed in BS patients with history of thrombosis [46, 47]. A decreased production of nitric oxide (NO), a prominent marker of endothelial dysfunction, has been reported in some patients with active BS [49] due to oxidative stress generated by inflammatory cells. Glu 298 Asp polymorphism of endothelial nitric oxide synthase (eNOS) might be a susceptibility gene in some BS patients and might explain the different susceptibility in the risk of thrombosis in certain ethnic populations of BS patients [50]. Discordant data on hyperhomocysteinemia have been reported in BS. However, most studies showed high plasma levels of homocysteine in BS patients with history of thrombosis, especially in the active phase of disease [51].

Controversial results were also found about the association of various procoagulant factors, such as coagulation factor V gene G1691A (factor V Leiden) and prothrombin G20210 mutations, with BS disease, suggesting that these mutations might be an additional risk factor for thrombosis in certain populations. For example, factor V Leiden mutation was found to be more prevalent in Turkish BS patients [52, 53], but not in Italian, Spanish and Israeli ones [54, 55]. Prothrombin gene mutation was not found to be relevant in several studies [57] but a recent

metaanalysis showed a significant association between the presence of prothrombin G20210A mutation and thrombosis in BS, when Turkish patients were excluded [55]. Elevated lipoprotein (a) levels could contribute to the development of thrombotic events in BS [58].

Instead, in most studies deficiencies of natural anticoagulant proteins including protein C (PC), protein S (PS) and antithrombin (AT) seem not to play a relevant role for thrombotic manifestations in BS patients [59]. Finally, some studies have shown defects in fibrinolysis [60, 61] and signs of enhanced platelet activation and increased level of platelet microparticles in BS patients compared with healthy controls [62].

Lower extremity DVT is the most frequent site for thrombosis, femoral (superficial, deep and common), popliteal and crural veins are mostly involved but thrombosis is possible at any vein sites [63] and occurs often in atypical sites. Cerebral sinus, upper limb, renal, hepatic and vena cava thromboses have been observed in BS patients [64]. BS should be always considered in the differential diagnosis of venous thrombosis in unusual sites in young men.

Moreover, BS may be a cause of superior (SVC) and inferior vena cava (ICV) thrombosis. This involvement makes up 9 and 4 % of all vascular complications and is sometimes associated with thrombosis of other sites [37]. SVC thrombosis may lead to swelling and cyanosis of face and arms and prominent venous neck collaterals. Pleura effusions and chylothorax rarely occur and the outcome is good [65]. IVC thrombosis may determine abdominal collaterals, oesophageal varices, hyperpigmentation and thrombosis that may extend to the hepatic vein [66]. Budd-Chiari syndrome is an uncommon condition (1–3 %) associated with a significant mortality rate, leading to death of about 50 % patients [67]. Cerebral venous thrombosis (CVT) occurs in 8 % of BS patients and represents 17–30 % of all central nervous lesions [68, 69]. Superior sagittal sinus and transverse sinus are involved in 60 % of cases. The most common symptoms of CVT, in descending of frequency, are headache, papilledema, fever, nausea, vomiting, and focal deficits. The prognosis is usually good and the most frequent complication is a severe visual loss due optic atrophy [70].

Superficial vein thrombophlebitis (SVT) is a characteristic clinical feature of BS and occurs in 2.2–20 % of BS patients and in some studies SVT has been also reported as the most common vascular lesion [71, 72]. SVT may occur in large and small veins of legs in the shape of a painful nodule often indistinguishable from erythema nodosum [38]. It is often associated with DVT, tends to recur, and may be a complication of venipuncture. SVT occurrence should be considered a risk factor for the development of future vascular events [26].

Intracardiac thrombus, containing inflammatory cell infiltration [73], located usually in the right ventricle, is a rare manifestation of BS. It occurs mostly in young men of the Mediterranean basin and the Middle East [74] and is strongly associated with pulmonary aneurysms [75] and other vascular involvements in any part of the body.

Management of vascular thrombosis in BS is based on immunosuppressive therapy to reduce inflammation of vessel wall along with the formation of thrombus. EULAR guidelines currently suggest immunosuppressive agents such as corticosteroids, azathioprine, cyclophosphamide, or cyclosporine A. Anticoagulants, antiplatelet therapy, or antifibrinolytic agents are not recommended especially in patients showing thrombosis coexisting with arterial aneurysms, because of the risk of serious bleeding [76]. According to the hypothesis that inflammation plays a major role in the development of thrombosis in BS, the successful use of anti-TNF-α monoclonal antibodies in the management of vascular complications has been increasingly reported. It may be an important therapeutic approach for patients with active disease resistant or intolerant to conventional immunosuppressive therapy. The rapid response and the good tolerability shown in these reports suggest that anti-TNF-α antibodies could be used as first-line treatment in severe disease [77, 78].

11.3 Atherosclerosis and Cardiac Involvement

BS is a vasculitis, characterized by inflammation of vessels (including arteries), with inflammatory cellular infiltration in the perivascular regions, and by the destruction of the media and by adventitial fibrosis, resulting in aneurysms, occlusions, thrombosis. Atherosclerotic lesions, with intimal hyperplasia, medial degeneration, and calcifications are rare in BS [79]. Several studies suggest that atherosclerosis is not much increased in BS patients, differently from other chronic autoimmune disorders such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), or other vasculitis such as Takayasu arteritis (TA) [80, 81]. Therefore, atherosclerotic cardiovascular disease, coronary artery, and cerebral events are not prominent features in BS manifestations [6]. On the other hand, recent studies have pointed out that signs of endothelial cell dysfunction (ECD), a condition widely regarded as the initial lesion in the development of atherogenesis, are present in blood from BS [82]. Endothelial injury agents such as vWF [46] and thrombomodulin were increased in blood from patients with active BS [83], as well as adhesion molecules such as E-selectin, produced by activated endothelial cells [84], suggesting that a pathological activation of endothelial cells occurs in BS. A decreased production of nitric oxide, that reflects endothelial dysfunction, has been also shown in BS patient. All these data suggest that ECD, resulting from vasculitis, could play a key role in the pathogenesis of thrombotic manifestations in BS patients. Endothelial function, tested by flow-mediated dilatation of brachial artery (FMD) was also found to be significantly impaired in BS patients [45] in many studies. Instead, conflicting results were published on subclinical atherosclerosis. However, whereas previous studies were not able to demonstrate relevant alterations of carotid arteries, more recently carotid intima-media thickness (IMT) has been reported to be increased in BS in comparison with matched healthy controls [80]. Thus, further clinical studies aimed to assess the true atherosclerotic burden in BS patients are necessary.

Clinical cardiac involvement in BS is observed in only 1–6 % of patients, but it has been found in 16 % of patients on pathological examination [41–85]. Heart manifestations include, in addition to intracardiac thrombosis, pericardial involvement, myocardium and endocardium complications, and coronary artery disease. Pericarditis is a common cardiac manifestation and may be present alone or associated with other cardiovascular diseases. It has a good prognosis, complications such as cardiac tamponade and chronic constrictive pericarditis being rare. Colchicines and immunosuppressive treatment have successful results [86, 87]. Endomyocardial fibrosis is not frequent but it is a characteristic manifestation of BS. Fibrosis primarily affects the right side of the heart and its association with other cardiac diseases such as intra-ventricular thrombosis, arteritis and valvulopathy is reported in some cases and it might be a result of endocarditis or myocarditis in some BS patients [88].

Aortic and mitral valve and coronary artery disease may be observed in BS patients. Coronary artery disease is mainly due to vasculitis and aneurysms and usually is not associated with atherosclerotic lesions [89]. The inflammatory process may involve arteries and arterioles of coronary system leading to silent ischemia, myocardial infarction, and functional abnormality [90, 91]. In few studies, diastolic dysfunction of left ventricle has appeared more pronounced in patients with BS than in controls. It is reported in 37 % of BS patients due to primary myocardial disease, alterations of coronary microcirculation or silent ischemia [92, 93]. Thus, this severe condition should be always investigated in BS patients [94]. Finally, cardiac conduction system may be affected by inflammation resulting in premature beats, ventricular tachycardia, AV block, right bundle branch block [95, 96].

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Intestinal Behçet Disease

12

Cristina Cenci and Monica Milla

Behçet disease (BD) is a rare, chronic, multisystemic, inflammatory syndrome with oral and genital ulcerations and ocular inflammation, relapsing uveitis, epididymitis and mucocutaneous, articular, gastrointestinal, neurologic, and vascular manifestations [1]. Classified as a systemic vasculitis, it can involve both the arteries and veins of almost any organ. This is an analysis of intestinal involvement in BD.

12.1 Prevalence

The frequencies of GI involvement vary among different ethnic groups and occur in 0–60 % of BD patients (Fig. 12.1) [2, 3].

Intestinal BD can affect various anatomical sites such as the esophagus, stomach, duodenum, jejunum, and colon [2]. Rectal involvement is particularly rare and occurs in less than 1 % of patients [3, 4]. Diarrhea (bloody or nonbloody), nausea, vomiting, and abdominal pain are the most common intestinal symptoms of BD [2, 5]. Other symptoms include gastrointestinal bleeding (GIB) and weight loss [6]. Intestinal involvement in BD is rare but significant because it is one of the most frequent causes of severe morbidity and fatality during the course of the disease [7]. Intestinal symptoms usually appear 4–6 years after the onset of oral ulcers [8] and sometimes, diagnosis has taken up to 7 years, especially in complicated cases of intestinal BD [9] (Table 12.1).

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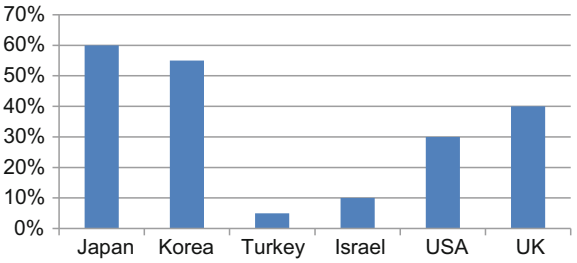


Fig. 12.1 Frequence of GI involvement by ethnic group (Reproduced with permission from [3])

Table 12.1 Gastrointestinal manifestations of Behçet disease (Reproduced with permission from [4])

Anatomic site(s)	Gastrointestinal manifestation(s)
Esophagus ulcers	esophagitis, fistulae, strictures varices[a]
Stomach, small intestine, colon	Ulcers[a]
Anal/rectal region	Ulcers,[a] fistulae, abscesses, proctitis, fissures
Liver	Budd-Chiari syndrome (acute, subacute, or chronic), fatty liver disease, hepatomegaly, congestion, cirrhosis
Spleen	Splenomegaly, congestion
Pancreas	Acute pancreatitis

[a]Ulcers are typically round, deep, and well demarcated, regardless of their location

Esophageal involvement is seen in 2–11 % of cases, but these statistics may be underestimated [2].

The oral ulcers of BD that occur at least three times a year are aphthous or herpetiform [2]. The lesions are generally hurting and heal with little scarring regardless of treatment. Moreover, the intermittent oral ulcerations of BD tend to be multiple and usually include the soft palate and oropharynx [2]. Smoking may reduce the gravity of ulceration in BD. Histologically, there is vasculitis with different infiltration: monocytes and lymphocytes in early disease and neutrophils in older lesions. Additional findings are both in early and late lesions: fibrinoid necrosis, endothelial swelling, and a perivascular infiltrate. Esophageal lesions respond well to high-dose corticosteroid (CS) therapy [3, 10].

The stomach is the least commonly affected part of the GI tract [8].

Duodenal BD is resistant to medical therapy and presents with aphthous ulcers. However, biopsies of the ulcers may reveal microthrombi of the mucosal vessels and, unlike classic chronic peptic ulcers, duodenal deformity is not seen [2].

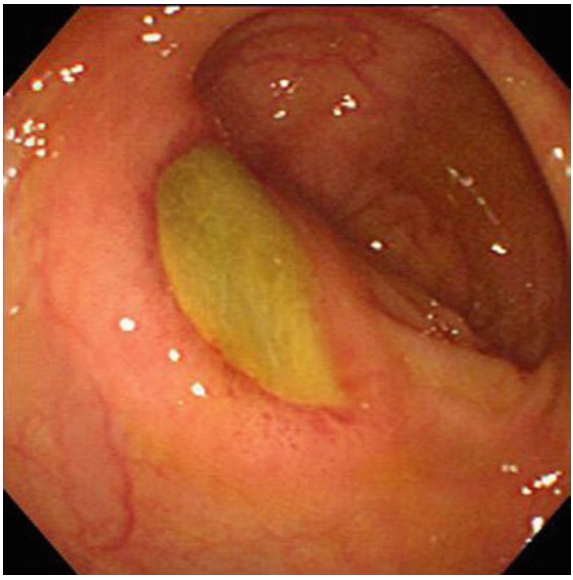


Fig. 12.2 Aphthous-type ulcer (Reproduced with permission from [36])

Intestinal BD often requires surgical intervention due to complications from perforations, fistulae, and considerable GIB, which happen in up to 50 % of patients [8, 11]. Patients with refractory colonic complications may often have both intestinal BD and IBD.

The colonic ulcers in BD have been classified as volcano-type, geographic, and aphthous. Volcano-type ulcers were described as deeply, well-demarcated, penetrating ulcers with nodular margins, converging folds, or pseudopolyps. Geographic-type ulcers were defined as thin ulcers with sharp edges. Aphthous-type ulcers were small, punched-out shallow ulcers.

Volcano-type ulcers have more frequent recurrences, a less favorable response to medical treatment and need surgery more frequently (Fig. 12.2).

Histologically, vasculitis of the small veins and venules is common in cases of intestinal BD. It is characterized by a lymphocytic infiltrate. There is a nonspecific chronic inflammation and a disruption of the submucosal connective tissue in Behçet's ulcers. Granulomas are absent. Intestinal BD may mimic CD when there are focal ulcers, fistulae, strictures, and the ileocecal location.

BD can also affect the liver, pancreas, and spleen [2]. Patients may present with hepatomegaly, ascites, edema, and abdominal and/or thoracic wall varices [8]. Patients can develop extensive intrahepatic and abdominal collaterals [2]. Budd-Chiari syndrome is an important extraintestinal manifestation that is related to a grave prognosis [12]. Splenic involvement has been described on autopsy in up to 22 % of patients with BD [13].

12.2 Assessment of Disease Activity

In 2011, Cheon and associates developed a Disease Activity Index for Intestinal BD (DAIBD; Table 12.2) [3]. Previously, intestinal symptoms had been judged using the Crohn's Disease Activity Index. The DAIBD is a moderately simple, 8-index scoring system that assesses clinical features in the preceding 7 days; it is useful and immediate because it does not require laboratory data or endoscopic findings [14].

12.3 Diagnosis

The diagnosis of BD is based on clinical features, as there is no specific laboratory test. In active BD levels of serum markers of inflammation may be elevated; however, these findings are not pathognomonic and may also be observed in many different situations as IBD or other forms of vasculitis. Patients with active BD often have elevated levels of serum immunoglobulin (Ig)D [1], of serum IgA and of complement levels [2]. Positive results from a pathergy test have limited reproducibility and vary significantly, depending on geographic location (60 % in Middle Eastern populations, 15 % in Korean populations, and 5 % in North American populations); it is aspecific and not associated with disease activity [1].

As regards the instrumental examinations a barium swallow study may be performed in patients with upper intestinal symptoms; however, superficial ulcers may be missed. Pyloric stenosis without duodenal deformity is a characteristic finding in BD with upper GI involvement [8]. Computed tomography (CT) scan/enterography, and magnetic resonance (MR) enterography are useful for diagnosing small bowel disease in intestinal BD, but these imaging modalities may not be regularly accessible [14, 15]. A double-contrast barium enema may be useful for identifying colonic lesions and determining their extent. Colonic haustra are typically preserved in patients with BD, unlike in patients with UC [2].

An endoscopic examination is necessary. Ulcers seen on colonoscopy are typically irregular, punched-out, large (>1 cm), single or few in number, deep and with discrete margins in a focal distribution [8]. Wireless capsule endoscopy may be useful for identifying ulcers in the small bowel [16]. Double-balloon enteroscopy may be essential in order to obtain small bowel tissue to establish a complete diagnosis [17].

12.4 Differential Diagnosis

Behçet's disease should be considered in the differential diagnosis in patients with recurrent orogenital ulcerations and enterocolitis with a nonspecific histological feature. GI manifestations of BD must be differentiated from those associated with infectious enterocolitis, intestinal tuberculosis (TB), IBD, other causes of colitis, appendicitis, and diverticulitis.

Table 12.2 Disease Activity Index for intestinal Behçet disease (Reproduced with permission from [4])

Clinical feature Score	Points
General well-being over the past week	
Well	0
Fair	10
Poor	20
Very poor	30
Terrible	40
Fever	
<38 °C	0
≥38 °C	10
Extraintestinal manifestations	5 per type of manifestation[a]
Abdominal pain over the past week	
None	0
Mild	20
Moderate	40
Severe	80
Abdominal mass	
None	0
Palpable mass	10
Abdominal tenderness	0
None	10
Mildly tender	
Moderately or severely tender	20
Intestinal complications	10 per type of complication[b]
Number of liquid stools over the past week	
0	0
1–7	10
8–21	20
22–35	30
≥36	40

[a]Five points are added for each type of the following manifestations: oral ulcers, genital ulcers, eye lesions, skin lesions, or arthralgia; 15 points are added for each of the following: vascular involvement or central nervous system involvement

[b]Such as a fistula, perforation, abscess, or intestinal obstruction

12.4.1 Crohn's Disease

It is often difficult to differentiate intestinal bowel disease (IBD) from intestinal BD because of the analogy of symptoms, endoscopic appearance, and intestinal manifestations. While granuloma is a pathologic hallmark of CD, it is not a typical lesion of BD just like cobblestoning and there is less inflammation around ulcer in BD compared to CD [8]. Deep ulcers associated with vasculitis are the most characteristic pathologic feature of BD [8]. The intestinal wall is of normal thickness, unlike the rigid, narrowed segments seen in CD. In addition, fistula formation and intestinal perforation tend to occur early in BD as compared to CD where they happen in a later course of the disease. Free perforation is rare in cases of CD but can occur in BD [18]. Scalloping, nodular patterns, and complications such as abscess formation are not observed in intestinal BD.

12.4.2 Ulcerative Colitis

Colonic BD occurs most frequently in the ileocecal. However, in ulcerative colitis the disease starts in the rectum and moves to the right colon, and also the ulcers are deeper in BD than ulcerative colitis [8]. Furthermore, there is a significant association with B52 and DR2 for patients with UC whereas B51 is not related (Fig. 12.3).

Epidemiological data regarding inflammatory bowel disease (IBD) and BD are very different, in particular, for World distribution. In fact BD is most prevalent

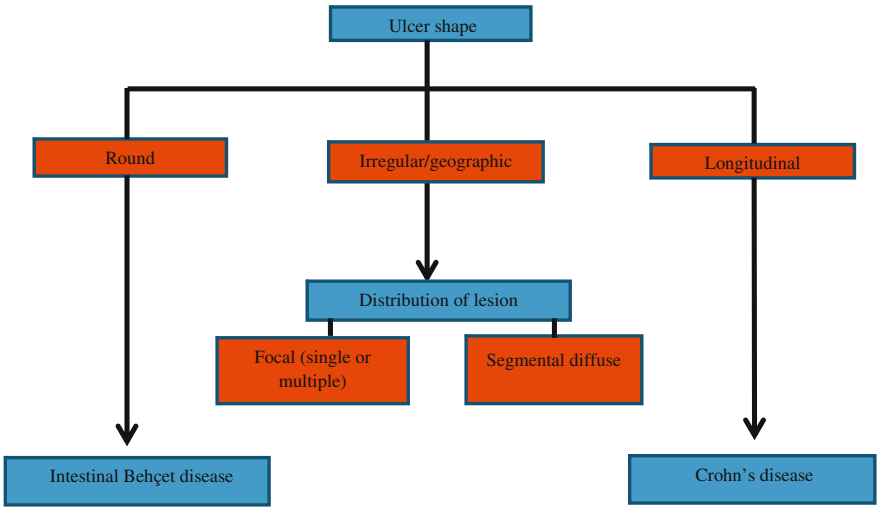


Fig. 12.3 Proposed classification scheme for differentiating between intestinal Behçet disease and Crohn's disease (Reproduced with permission from [11])

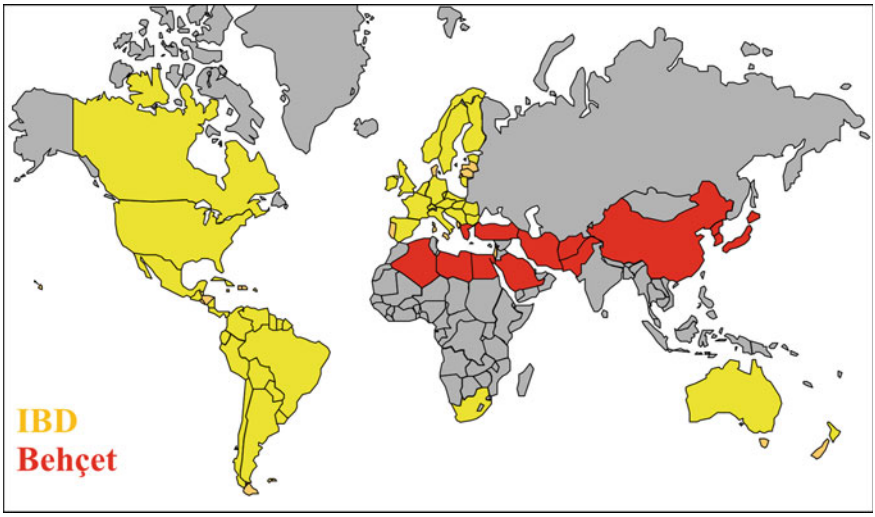


Fig. 12.4 The World distribution of BD and IBD (Reproduced with permission from [4])

along the Silk Road, an ancient trading route between the Mediterranean and East Asia while IBD is predominant in Western countries with greater economic development (Fig. 12.4).

12.4.3 Steroid and Nonsteroid Anti-Inflammatory Drug-Induced Damage

Steroid and nonsteroid anti-inflammatory drug—(NSAID—) induced damage involves mostly proximal large intestine and happens in various forms including colitis, colonic ulcers, pseudomembranous colitis, collagenous colitis, bleeding, and perforation, while aphthous ulceration is very rare. It may occasionally involve small intestinal with ulcers, perforation and strictures that need surgery. The patient's clinical history is important since many patients with BD use steroids to control their disease. The BD ulcers differ from steroid-induced ulcers both in size and appearance. Steroid-induced ulcer is usually single while the ulcers of BD are characterized by multiple perforations. In one study, the frequency of intestinal perforation in patients with BD on steroids was 41 %. Also in cases of BD without a history of steroid use, intestinal perforation can occur in up to 33 % of the patients [8].

12.4.4 Amebiasis

In the Middle East the differences of amebiasis and BD are important since both occur frequently. Endoscopically, the disease is diffuse in both conditions, and the

mucosa is hyperemic and is characterized by deep ulcers. However, the presence of an amoeba in a fresh stool specimen is the best way to differentiate the two conditions [8].

12.4.5 Tuberculosis

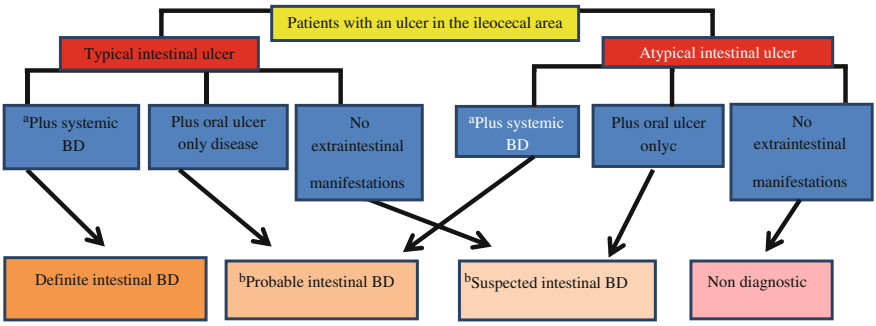
Intestinal TB may be difficult to distinguish from intestinal BD and CD both clinically and endoscopically.

Patients with intestinal TB often present with right lower quadrant abdominal pain, fever with night sweats, anemia, and weight loss [8]. A T-SPOT TB blood test may be a useful tool for diagnosing intestinal TB [19]. Discriminating intestinal BD from intestinal TB is particularly important in geographic regions where both diseases are common, as treatments for the two diseases are completely different [14]. Biopsies obtained during colonoscopy for culture and polymerase chain reaction testing for *Mycobacterium tuberculosis* can help to determine the appropriate diagnosis [14] (Table 12.3).

12.5 Role of Serum Antibodies

Various autoantibodies have been described in IBD, specifically perinuclear antineutrophil cytoplasmic autoantibody (pANCA) in UC and anti-*Saccharomyces cerevisiae* antibody (ASCA) in CD. ASCA is directed against the oligomannosidic epitope of the yeast *S. cerevisiae* and is positive in 40–70 % of patients with CD, 10–15 % of patients with UC, and 0–5 % of healthy control subjects [6]. ASCA positivity may be establish in up to 44 % of patients with intestinal BD but only

Table 12.3 Algorithm for the diagnosis of intestinal Behçet disease (BD) (Reproduced with permission from [4])



[a]Subtypes of systemic BD were classified according to the diagnostic criteria of the Research Committee of Japan
[b]Close follow-up surveillance is necessary

3–4 % of patients with nonintestinal BD and 9 % of healthy control subjects [6, 20]. ASCA positivity is associated with an increased number and frequency of operations in patients with intestinal BD [6]. pANCA is positive in 60–80 % of UC patients and 10–30 % of CD patients. In a Turkish study involving 18 patients with known BD, none were pANCA-positive [21]. Antiendothelial cell antibody (AECA) has been detected in patients with BD [21]. Anti α-enolase antibody is a target protein of serum AECA in BD patients and may be associated with disease activity and severity [21].

12.6 Prognosis and Treatment

The global prognosis in intestinal BD is more guarded than in CD. Remission rates with medical therapy are similar to those achieved in CD patients, but recurrence rates are higher and patients require surgical intervention more frequently in intestinal BD [14]. Poor prognostic factors include volcano-shaped ulcers, higher CRP levels, history of postoperative CS therapy, presence of intestinal perforation on pathology, extensive ileal disease, presence of ocular disease, and positive ASCA status [6, 22].

Prognosis of BD runs a chronic, unpredictable course with exacerbations and remissions which decrease in frequency and severity over time. The cause of death is more frequently connected to major vessel disease and neurological involvement. The prognosis is poor for young males. Treatment of BD is usually palliative and symptomatic. The preferred treatments are combined drug therapy with any or all of the following: steroids, NSAIDs, immunosuppressives, and cytotoxic agents. Complete remission is achieved in 38 % of patients with intestinal BD after 8 weeks of medical treatment. Surgery is the other modality of treatment.

In patients with severe uveitis and intestinal BD, colectomy is indicated to improve uveitis in a few cases. In another case, a patient with refractory intestinal BD and pyoderma gangrenosum underwent a total colectomy, resulting in rapid improvement of the pyoderma gangrenosum [23].

The medical treatments used for intestinal BD are often the same to those used for IBD. Sulfasalazine (1–4 g/day) or mesalamine (5-aminosalicylic acid [5-ASA]; 2–4 g/day) and CSs are the main therapies used to treat intestinal BD. However, 5-ASAs should only be used to treat intestinal BD if clinical and endoscopic activity are mild. CSs are often first-line therapy during the acute phase of intestinal BD or in patients with severe systemic symptoms or moderate/severe disease activity [14]. The dosage of oral CSs depends on the severity of the lesions and ranges from 20 to 100 mg/day of prednisolone [1]. Intravenous pulse doses of methylprednisolone (1 g/day for 3 days) may be used if necessary [14].

Approximately 46 % of patients have complete remission 1 month after starting CS therapy, but 43 % only have partial remission, and 11 % have no response [24]. At 3 months, prolonged response to CS therapy drops to 41 %; in addition, 46 % of patients are CS-dependent, and 7 % require surgical intervention [24].

Many patients become CS-resistant or CS-dependent.

Azathioprine (2.0–2.5 mg/kg/day) has been used in intestinal BD to help reduce the dose of CSs and, in some cases, to completely stop CS therapy. Confirmed endoscopic remission was seen in 75 % of azathioprine-treated patients, with a 32-month median duration of remission. Azathioprine appears to be more effective in women ($P = 0.014$) for unknown reasons [25]. Patients with intestinal BD have also been successfully treated with thalidomide (2 mg/kg/day), with this drug achieving symptom control and alleviating CS dependency [26]. Similar to its use in CD, etanercept has not been shown to be beneficial in patients with intestinal BD [27].

TNF-α is an important agent in the inflammatory process observed in BD; therefore, infliximab, a chimeric monoclonal antibody to TNF-α, is beneficial in patients who are unresponsive to conventional therapies. Treatment of intestinal BD usually requires a combination of medical and surgical therapies, much like the treatment of IBD.

Infliximab has been shown to be effective for induction and maintenance treatment in patients with severe mucocutaneous, intestinal, and ocular manifestations of BD [28]. The standard dosage of infliximab for treatment of intestinal BD has not been established; therefore, the treatment dose and protocol for CD are typically used [28]. Maintenance infliximab treatment has been shown to be more beneficial than short-term treatment for maintaining remission in patients with intestinal BD [29]. Patients on anti–TNF-α agents must be monitored closely for infections, malignancies, demyelinating diseases, and congestive heart failure. Table 12.4 lists groups of patients with BD who may benefit from anti–TNF-α therapy [30].

The first three groups of patients typically have severe disease and are likely to benefit from anti–TNF-α therapy. Severe disease is defined as two or more relapses of posterior uveitis or panuveitis per year, low visual acuity due to chronic cystoid macular edema, and active central nervous system parenchymal disease.

Table 12.4 Patients with Behçet Disease who may profit from Anti−Tumor Necrosis Factor (TNF)-α therapy (Reproduced with permission from [4])

Patients who have a definite diagnosis of Behçet disease:
1. Patients who have active disease, including objective signs of inflammation
2. Patients who have failed treatment with drugs that have a documented efficacy for controlling Behçet disease manifestations; these patients may also have taken low-dose corticosteroids (equivalent to a prednisolone dose $\leq$ 7.5 mg/day)
3. Patients who have contraindications or intolerance to conventional therapeutic regimens
4. Patients who do not have contraindications to anti–TNF-α treatment
5. Patients with intestinal inflammation, chronic arthritis, and/or mucocutaneous manifestations that significantly impair quality of life

The first case of BD treated with infliximab was reported in 2001 [31]. Infliximab led to rapid and complete resolution of the patient's intestinal and extraintestinal symptoms, and this benefit was maintained even after CS discontinuation [31]. Intestinal BD has also been successfully treated with adalimumab a fully human IgG1 monoclonal antibody that binds to TNF-α [32]. Intestinal manifestations of BD appear to have a more sustained response to anti–TNF-α therapy than other manifestations of BD [33]. Despite several case series showing the efficacy of anti–TNF-α agents in intestinal BD, a prospective, randomized, placebo-controlled trial is needed to validate these findings.

It is also described an anecdotal successful treatment of a child with severe/refractory intestinal Behçet disease, by lymphocyte-depleted autologous stem cell transplantation (ASCT) following high-dose immunosuppressive therapy (HDIT) [34].

Indications for surgery include severe GIB and abdominal pain for persistent bleeding or perforation, fistulae, obstructions, abdominal masses, and failure to respond to medical therapy [22]. Creation of a stoma is often chosen over primary anastomosis, due to the high rates of intestinal leakage, perforation, and fistula formation at the anastomotic site [8]. It is not established at the moment of surgery and length of bowel resection [14]. Disease recurrence is seen in 40–80 % of patients and is often found at or near the anastomotic site, as with CD [7, 22]. Up to 80 % of patients with disease recurrence require an additional operation [1, 8].

Follow-up radiographic and endoscopic imaging should begin within 2 years after surgery, with initiation of early medical treatment if disease activity is present [8].

Extensive ileal disease and ocular lesions are signs of increased disease severity and risk of surgical resection [35]. Volcano-shaped ulcers, elevated CRP levels, and the presence of intestinal perforations on pathology are independent predictive factors for relapse [22].

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Audio Vestibular Involvement in Behçet's Disease

13

Paolo Vannucchi and Rudi Pecci

The audio-vestibular system is often involved in many autoimmune syndromes as Cogan's syndrome and Granulomatosis with polyangiitis (Wegener's granulomatosis) but an involvement in Behçet's disease is reported more frequently only in the last years. Behçet's disease was first defined by Hulusi Behçet in 1937. It is a refractory multisystem disorder mainly presenting with recurrent oral aphthae and genital ulcerations, skin lesions, and uveitis. The disease is a chronic inflammatory disorder involving the small vessels, which is of unknown etiology. It has a worldwide distribution with a prevalence ranging from 1:1,000 to 1:10,000 in Japan and Turkey to 1:500,000 in North America and Europe. The aetiopathogenesis is obscure but Behçet's disease is considered to be immune-mediated.

Audio-vestibular disturbance, including hearing impairment, tinnitus, and dizziness, is one of the multisystemic characteristics of Behçet's disease.

There are studies and case reports in the literature about the inner ear involvement, sudden cochlear sensorineural hearing loss (SNHL) and incidence of SNHL in Behçet's disease. In these studies, the incidence of HL has been reported as 12–80 %.

Auditory and vestibular lesions, among the clinical manifestations of central nervous system (CNS) involvement, were first described by Alajouaine et al. [1]; the authors described SNHL and gaze paretic nystagmus in a patient with Behçet's disease suffering from meningoencephalitis. Since then, other authors have shown that SNHL and dizziness are frequent symptoms in patients affected by Behçet's syndrome with or without the involvement of the CNS. Erdinç et al. [2] suggest

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that presence of SNHL in Behçet's disease is prevalent and represents a fourth clinical symptom after oral, genital ulcers, and skin lesions: a statistically significant SNHL at high frequencies when compared with the speech frequencies has been reported and this high incidence of SNHL can be attributed to small venous disease that is seen in the majority of neuro-Behçet patients. Kulahli et al. [3] carried out a study to determine the characteristics and incidence of SNHL and vestibular disturbance in Behçet's syndrome with a large number (62) of patients, and they found that (1) the hearing and vestibular disturbances in Behçet's syndrome are more prevalent than previously recognized, (2) SNHL in high frequencies in Behçet's patients is an indicator of cochlear involvement, (3) there is a higher prevalence of central vestibular syndrome in Behçet's patients than it was thought before, and (4) HLA-B51 antigen may be able to be a prognostic factor for SNHL in Behçet's patients.

Behçet's disease is typically characterized by a lack of correlation between other organs and audio-vestibular involvement, which is in keeping with the multifocal nature of the disease process. Also, a lack of correlation was found between the auditory and vestibular lesions, but this may be explained by an understanding of the vascular supply: the common cochlear artery and anterior vestibular artery are the main branches of the labyrinthine artery and can be selectively involved by immunologically mediated inflammation. Furthermore, the incidence of dizziness is often more common than audiologic symptoms, probably due to the more diverse causes of dizziness, including peripheral and central vertigo.

In an interesting study, comparing Behçet's patients with sex and age matched healthy subjects, Süslü et al. [4] showed that in younger patients there could be a lesser ratio of SNHL compared to older ones. However, although hearing thresholds were within the normal limits according to pure-tone average—PTA- (at 500, 1,000, 2,000, and 4,000 Hz), hearing levels of the patients with Behçet's disease were found to be higher than the controls at most of the single frequencies and differences were seen to be significant. Furthermore, in the high frequencies (9,000–16,000 Hz) 63.4 % of the patients had hearing loss and the differences between the hearing levels of patient and control group tend to increase definitely in high frequencies. This finding points a cochlear involvement in Behçet's disease beginning and prominent in basal turn of the cochlea. In these patients it also could be found decreased responses with otoacoustic emission (OAE) and lower values of signal to noise ratio (SNR); this means that the physiological motility of the outer hair cells of the patients with Behçet's disease is lesser than the normal subjects. Meanwhile, normal hearing thresholds together with the decreased OAE responses could be accepted as the early findings of sub-clinical cochlear involvement in Behçet's disease. Finally, not only the duration of the disease, but also clinical features or other system involvements usually do not correlate with hearing levels. These data show that cochlear involvement can be regarded as an early sign and takes place even in patients without significant organ involvements.

Erbek et al. [5] suggest an association between delayed vestibular evoked myogenic potentials responses (VEMP) and Behçet's disease. Prolonged VEMP responses in patients with Behçet's disease maybe explained by chronic

inflammation involving the pathways of the sacculo-collic reflex. Since abnormal VEMPs are not always associated with caloric weakness, it can be speculated that inferior and superior vestibular nerves might be damaged separately in Behçet's disease. Therefore, the VEMP response may be a useful diagnostic tool for vestibular evaluation in this disease.

Even Cinar et al. [6] more recently revealed that the prevalence of SNHL was significantly higher in the Behçet patients than in the controls. The duration of Behçet's disease had no significant impact on whether patients did or did not experience hearing loss. The authors reported hearing loss was the fourth most common clinical finding in the Behçet group, after oral ulcers, genital ulcers, and skin lesions, and they suggest the need for an adequate investigation of hearing in the routine follow-up of these patients.

Indeed, Behçet's disease may present with features other than the classic triad of symptoms. Raised awareness of the clinical features within the head and neck region will hopefully enable early diagnosis and treatment of this potentially serious condition.

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Behçet's Syndrome and Gynecological Manifestation in Reproductive Age and Pregnancy

14

Maria Elisabetta Coccia and Tommaso Capezzuoli

14.1 Definition and Etiology

Behçet's syndrome (BS) is a multisystem inflammatory chronic disorder, characterized by relapsing oral and genital ulceration. The eyes, joints, skin, central nervous system (CNS), vascular system, and gastrointestinal tract are also often involved by the inflammatory process. Classified as a systemic vasculitis, BS can involve both the arteries and veins of almost any organ [1].

Some symptoms of BS were first described by Hippocrates and later by Bluthe in 1908 [2], but only in 1937 Hulusi Behçet, a Turkish dermatologist, first identified and described the three main clinical signs represented by recurrent oral aphtae, genital ulcerations, and recurrent anterior uveitis [3].

BS etiology is uncertain, even if it has been hypothesized as a genetic predisposition determined by HLA-B51 allele. Infectious agents may also play a role as pathogenic triggers in genetical predisposed individuals. BS natural course is characterized by relapse and remission [4].

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14.2 Epidemiology

BS was classically described along the historical Silk Road, going from East (China) to West (Spain and Portugal). Actually, due to immigration, BS could be diagnosed in several countries worldwide, with a prevalence ranging from less than one case to 370/100,000 inhabitants in Turkey.

Recent epidemiological data show that BS is more frequent than reported in the past: 7.2 in 100,000 inhabitants in France, 4.2 in Germany, 8.6 in the USA, and 80 in Iran [5].

Women appear to be less frequently affected than men (the male to female ratio is 7:1 in symptomatic forms) and when affected show a less severe pattern of disease. Sex ratio is even reported higher in the poorer countries, where probably women are reluctant to consult a physician for genital aphthosis because of cultural or social aspects.

The mean age of onset of BS is most commonly seen at the third decade, although the age at which the final diagnosis is achieved is usually at the fourth decade.

14.3 Genital Ulcers

The mucocutaneous involvement is very frequently encountered in BS patients, since most of them show oral and genital aphthosis, pustules, papules, or erythema nodosum [6].

Regarding genital aphtosis in particular, there are differences in prevalence between the various countries: 65 % of patients in Iran, 73 % in Japan, 76 % in China, 83 % in Korea, 64 % in Germany, 88 % in Turkey, 86 % in Morocco, 87 % in Tunisia, 89 % in Britain, and 97 % in the U.S. [5].

Morphologically, they are similar to mouth ulcers and initially manifest as papules or pustules that later evolve into frank ulcers. The latter are usually painful, superficial, well-demarcated, and have an edematous border and a yellow fibrin-covered base. The ulcers can become secondarily infected and this complication can be kept in mind if topical glucorticoid are prescribed. The ulcers of BS frequently heal by scarring and the presence of these scars can be reported as suggestive of previous ulceration when BS is suspected. The scrotum is the most frequently involved site in males but ulcers on the shaft and glans penis are notable. However, whenever the glands penis is predominantly affected and scrotum is not affected, an underling HLA-B27 spondiloarthritis or a reactive arthritis should be suspected. In females, genital ulcers most commonly occur on the vulvae, major and minor labia, but the vagina and cervix can also be affected [7–11].

Moreover, micro-traumatism during sexual intercourses often triggers genital ulcers. This pathergy-like phenomenon creates an obvious impairment to normal sexual life due to pain during intercourse. Intense pain due to genital ulcers can also impair other daily activities such as sitting down or walking or determine dysuria during miction [12, 13].

It is reported that vaginal ulcers may be complicated by bladder or urethral fistulae. Groin, perineal, and perianal ulcers were occasionally described in adults or children with BS [14, 15]. However, we strongly recommend performing a colonoscopy procedure whenever this pattern of perineal involvement is prominent to rule out Crohn's disease, considering the frequent overlap between inflammatory bowel diseases and BS symptoms.

14.4 Genital Ulcers: Differential Diagnosis

Recurrent genital ulcers may be associated to some diseases other than BS. In herpes simplex infection, lesions grow up as multiple, painful, small, grouped vesicles on an erythematous base, recurring often in the same localization. Other conditions to consider in the differential diagnosis by BS genital ulcers are erythema multiforme and fixed drug eruption. Even sexually transmitted diseases may occur in the form of recurrent genital ulcer. In particular, syphilis, chancroid, lymphogranuloma venereum, and HIV infection should be especially considered [16].

The presence of genital ulcers may also be the hallmark of other autoinflammatory/autoimmune conditions: Hyper IgD syndrome, PAPA syndrome (pyogenic arthritis, pyoderma gangrenosum and acne), and MAGIC (mouth and genital syndrome with inflammatory cartilages) can actually present with similar genital lesions. In all these cases history taking and the presence of other associated symptoms usually guide the clinician to achieve the correct diagnosis.

14.5 Genital Ulcers: Management

Treatment of patients with BS in general requires a very close collaboration between different specialists in oral medicine, dermatology, ophthalmology, internal medicine, and neurology.

Genital ulceration is usually treated with topical corticosteroids and antiseptic agents as a first line usually for a period of 7–10 days. In case of very painful lesion, topical anesthetic, such as lidocain cream, can also be used. Topical sucralfate suspension is an alternative treatment for aphthous ulceration, while the local injections of glucorticoids (triamcinolone 0.1–0.5 mL) can be considered for refractory cases [16].

Several drugs have been used for treating BS patients with severe genital aphtosis.

Colchicine (1–2 mg/die) is often used as a first choice drug in treating mucocutaneous involvement in BS owing to its overall good toxicity and safety profile. Two randomized control trials (RCT), that addressed colchicine efficacy in BS, produced discordant results, since only one of them showed improvement in genital apthosis, particularly in women [17, 18].

Glucocorticoids are usually considered to treat severe and active disease, since they are very fast. An RCT of intramuscular metylprendisolone (40 mg every 3 weeks for about 6 months) however, failed to produced any benefit in occurrence of orogenital aphtosis in patients with active BS [19].

Azathioprine is the preferred agent to treat BS with ocular or central nervous system involvement, usually at a dosage of 2–3 mg/die. An RCT showed efficacy of this drug for controlling also mucocutaneous and orogenital lesions [20]. Screening of thyopurine S-methyltransferase blood levels, when available, is recommended before starting azathioprine therapy, since low enzyme levels are associated with an increased toxicity risk. In such cases azatioprine should not be administered and an alternative immunosoppressant should be used.

Since Methotrexate (10–20 mg/week) also showed some efficacy regarding mucocutaneous BD, it may be considered an alternative drug whenever azathioprine is not tolerated [21].

Cyclosporine at the dosage of 10 mg/kg/die has been shown to be superior to colchicine (1–2 mg/die) for treating aphtosis in BS. However, this very high dosage is not commonly used in clinical practice, since it is more associated to an increased risk of hypertension and kidney dysfunction. Moreover, considering its potential neurotoxicity, the drugs should be avoided in BS patients with overt or suspected CNS involvement [22, 23].

Dapsone at the dosage of 100 mg/die demonstrated some improvement of orogenital lesions in a single RCT, however, the small number of subjects prevent to draw definite conclusions regarding this drug [24].

Thalidomide has also been tested at the dosage of 100 mg/die. Some improvement in orogenital ulceration has been observed, however, erythema nodosum lesions were described to get worse in this trial [25]. Risk/benefit ratio has always to be carefully considered before using this drug, considering its high teratogenic potential for women exposed at childbearing age, who need a mandatory and effective contraception, and the possible development of peripheral neuropathy during such therapy.

Interferon-α showed efficacy in reducing orogenital ulceration. However, considering the frequent side effects, this therapy in clinical practice is usually reserved for patients with severe and sight-threatening ocular involvement [8, 26, 27].

Anti-TNF agents such as infliximab or etanercept have been used with success for controlling the most severe manifestations of BS [28–30]. However, the use of biological agents in treating mucocutaneous symptoms is not currently justified considering the high costs of such therapies.

14.6 Behçet's Syndrome and Pregnancy

Studies evaluating the effect of pregnancy on BS (remission or exacerbation) have obtained discordant results.

Uzun et al. in 2003 reported that in a population of 28 women (44 total pregnancy), remission rate of BS was 52.3 % (23 pregnancies) and exacerbation rate 27.3 % (12 pregnancies), while nine pregnancies remained unchanged [31].

Jadaon et al. described that remissions were significantly more frequent than exacerbations (observed only in one-sixth of the patients) during both pregnancy and postpartum period in 31 women suffering from BS [4].

An older study found that in 27 patients suffering from BS, 66 % showed a remission and 33 % showed an exacerbation of the disease during the pregnancy [32]. However, a more recent study confirmed this latter data and the fact that BS in general does not affect pregnancy outcome [33].

For patients with BS suffering a disease flare during pregnancy, the most frequent manifestations are usually represented by mucocutaneous ulcerations or arthritis [34, 35].

Furthermore, the literature reports several thrombotic episodes occurring during pregnancy or postpartum period in women suffering from BS. In particular, cerebral venous thrombosis [36], deep vein thrombosis [37], intracardiac thrombosis [38], and others have been described.

Cases of necrotizing villitis and decidual vasculitis have also been reported, determining both positive and negative pregnancy outcomes [39].

The variability of BS pregnancy may be determined by hormonal and immunologic changes typical of the gestation. In particular, it has been suggested that remissions may be maintained by placental immunosuppressive activity [4]. In fact, during the physiological pregnancy, both cellular and humoral branches of the immune system are suppressed, to permit the implantation of the paternal semiallogenic embryonic graft [32].

Probably, higher estrogenic levels typical of the pregnancy could induce inhibition of specific immune activities [40]; furthermore, other hormones such as progesterone, human chorionic gonadotropin, and α-fetoprotein could be implicated in the immunosuppressive condition [41].

Finally, it was reported a depression of neutrophil chemiotaxis and adherence function [42].

The impact of BS on fetal outcomes is actually not well-defined. Jadaon reported a higher rate of cesarean section and miscarriage in women suffering from BS [4], while another study detected a similar pattern of pregnancy complications in affected women when compared to control [13].

The etiology of thromboembolic events in BS is also not clear. There are conflicting results in the literature on the role of protein C, protein S, antiphospholipid antibodies, and factor V Leiden [43]. Other additional factors suspected to be implicated in thromboembolic events are impaired function of endothelial cells and anti endothelial cells autoantibodies [44]. Anyway, it must always be kept in

mind that BS patients have a higher risk of thrombosis/thrombophlebitis compared to normal controls, and this thrombophylic status can be unmasked during pregnancy.

14.7 Pregnancy Management in Behçet's Syndrome

The management of pregnancy in patients with BS is similar to that of other forms of systemic vasculitis, since both the disease activity and the concomitant use of particular immunosuppressive drugs can affect the pregnancy outcome.

As for other autoimmune disease, pregnancy should ideally be planned after a period of prolonged remission has been achieved. Behçet patients' pregnancy should also always be approached with a multidisciplinary team, including a rheumatologist/immunologist and a high-risk obstetrician. The mother and the fetus should be monitored and followed periodically [34, 45].

Diagnosis and evaluation of BS in pregnancy are difficult for some reasons:

- Acute phase reactants could be an unreliable indicator of inflammation because C-reactive protein and erythrocyte sedimentation rate are often elevated in pregnancy, also in the absence of vasculitis [46, 47].
- Radiologic assessments during pregnancy are necessarily limited [34].

In the evaluation of BS during pregnancy two points are important:

- Some infections can mimic vasculitis manifestations and their presence should be always investigated [48].
- BS course during previous pregnancy is not indicative of the following period [49, 50].

The drugs most commonly used in the treatment of systemic vasculitis are glucocorticoids, cyclophosphamide, methotrexate, and azathioprine.

Glucocorticoids are even today utilized as primary treatment in systemic vasculitis and they can be administrated at low dose during pregnancy [51].

Colchicine has also been reported to be safe during pregnancy, owing mainly to the consistent data obtained by familial Mediterranean fever women exposed to this drug during pregnancy for keeping disease control. Some caution in using it in pregnancy is, however, still required [52].

Cyclophosphamide is contraindicated during the first and second trimesters of pregnancy but it can be utilized in the third trimester in severe forms of disease, if its use is considered necessary [53]; intravenous immunoglobulin can be administered instead of cyclophosphamide in some cases, but they are usually not used for treating BS [34].

Among antimetabolites, methotrexate is considered as category X drug during pregnancy, since it can induce skull and limb abnormalities. Women who plan a pregnancy are recommended to suspend methotrexate therapy at least 3 months before conception [54].

On the other hand, azathioprine (AZA) seems to be better tolerated during pregnancy, since no specific pattern of congenital abnormalities has been observed in patients with systemic lupus erythematosus or in transplant recipient patients treated with this drug [53].

In conjunction with glucocorticoids, it represents the first choice drug when a moderate immunosuppression is required to treat ocular or neurological flares during pregnancy.

Mycophenolate mofetil (MMF) is also considered a category X proven teratogenic drug, since specific patterns of congenital defects have been reported. A distinctive MMF embryopathy has been in fact identified and described as the "EMFO tetrad": Ear (microtia and auditory canal atresia); Mouth (cleft lip and palate); Fingers (brachydactyly fifth fingers and hypoplastic toenails); and Organs (cardiac, renal, CNS, diaphragmatic and ocular) [55]. For these reasons women who are going to plan a pregnancy are recommended to stop MMF at least 6 weeks before conception and if an immunosuppressive drug is required to control disease activity AZA represents a reasonable and safer choice.

Data regarding anti-TNF agents are derived mainly by patients with rheumatoid arthritis, spondylarthritis, and inflammatory bowel disease [56, 57]. Even if such data do not clearly indicate a susceptibility to miscarriages or congenital abnormalities in exposed patients compared to controls, it seems reasonable to suspend such therapy during the first trimester or as soon as pregnancy has been detected, if not strictly necessary for ocular flares control.

14.8 Conclusion

Behçet's disease remains an elusive disorder, characterized by variable clinical presentations, organ involvement, disease course, and most important by different outcomes.

From the gynecological point of view, we can support the knowledge that genital ulcers can be easily diagnosed (and then treated) because of their typical morphological aspect.

Regarding pregnancy in BS, we advise women about the need to strictly follow the disease course during this time with the help of a multidisciplinary team, evaluating both disease status and fetal health.

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Pediatric Onset of Behçet Syndrome

15

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15.1 Definition and Classification

Behçet syndrome (BS) is a chronic relapsing multisystem vasculitis named after the Turkish dermatologist Hulusi Behçet, who reported the triad of recurrent oral aphthous ulcers, genital ulceration, and uveitis [1]. In 1990, the International Study Group defined the currently addressed diagnostic criteria for BS [2]. According to these criteria, diagnosing BS requires the presence of recurrent oral aphthous lesions plus two of the following symptoms: recurrent genital ulcers, eye lesions (uveitis or retinal vasculitis), skin lesions (erythema nodosum, papulopustular lesions, or acneiform nodules), and a positive pathergy test [2]. However, these criteria make no specific reference to pediatric onset BS and have never been validated in children.

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15.2 Epidemiology

The frequency of BS varies from one geographical area and ethnic group to another. Most BS cases are clustered along the historic *Silk Road*, extending from Japan to Mediterranean countries [3]. The highest prevalence of BS is reported in Iran (68/100,000) and Turkey (42/100,000) [4, 5]. A report from France showed that BS was much more common than had previously been appreciated among adult vasculitides [6]. BS may be observed before 16 years of age in 4–26 % of cases [7]. *Pediatric* BS occurs in less than 8 % of patients [8]. Ozen et al. [9] proposed that the prevalence is less than 10 cases per 100,000 children. However, data from a French epidemiological survey, indicated a prevalence of 1/600,000 in children under 15 years of age [10].

In some studies on childhood BS, males were found to be more affected [10–13]; while two studies (one from Japan and other from Turkey) reported a female predominance among children with BS [14, 15].

15.3 Genetic Background

Familial aggregation of BS was found to be high especially in the pediatric group [16, 17]. Gul et al. showed that the risk of the sibling of a patient with BS also having BS was 4.2 % [18]. An interesting study by Mahr et al. has shown that BS rate among North African immigrants in France was comparable with rates reported from North Africa [6]. All these data supported the genetic basis for BS.

Susceptibility to BS is reported to be strongly associated with HLA-B51 in different ethnic groups [3, 19–21]. However, most HLA-B51 carriers never suffer from BS in their lifetime and half of the BS patients are HLA-B51 negative [3, 22]. The highest contribution of the HLA-B51 to the overall genetic susceptibility to BS is estimated to be around 20 % [23]. A recent metaanalysis has shown that in BS, HLA-B51/B5 carriage predominates in males and is associated with moderately higher prevalences of genital ulcers, ocular and skin manifestations, and a decrease in prevalence of gastrointestinal involvement [24].

Recently, two large genome wide association studies (GWAS) conducted in Turkey and Japan confirmed the association with HLA-B51 and identified non-HLA single nucleotide polymorphisms (SNP) of interleukin-10 (IL-10), and IL-23R-IL-12Rβ2 regions associated with BS [25, 26]. More recently, another GWAS among the Korean population identified *GIMAP* cluster which is involved in T cell survival as a novel susceptibility locus for BS [27]. There are many association studies in Behçet disease, however, they have been carried out in small populations and/or lack functional studies.

Alternatively a pathway-based approach is powerful as it provides insight into how multiple genes may contribute to the pathogenesis of a disease. Four candidate causal SNPs and 11 pathways were found to contribute to BS susceptibility in a pathway-based analysis of BS GWAS datasets [28]. The highest ranked pathways were mostly driven by the HLA genes [28].

15.4 Etiopathogenesis

Although the etiopathogenesis of BS remains unknown, it is thought to involve a complex interaction of genetic, immunological, and environmental factors [29]. The episodic course of the disease, the lack of autoantibodies, and the inflammatory nature and the flares of the disease have led to the classification of BS as an autoinflammatory disease [30]. MEFV mutations causing FMF, another *autoinflammatory* disorder, have been reported to be more frequent among BS patients rising the hypothesis that they act as modifier or susceptibility factors [31, 32]. Another hypothesis is that an infectious agent (e.g., Herpes Simplex Virus 1, Parvo B19, and streptococcus) acts as a trigger of an abnormal immune response in genetically susceptible individuals [33]. Activation of $\gamma\delta$ T cells in BS patients was evident with different kinds of microorganisms [34, 35].

Heat-shock proteins (HSP) have been implicated in the pathogenesis of BS. HSP 60 acts as a danger associated molecular pattern (DAMP) molecule stimulating production of proinflammatory cytokines and development of a T helper 1 (Th1) immune response through tall-like receptor (TLR) 2 and 4 [36, 37]. High homology between human HSP 60 and the corresponding bacterial HSP 65 have been reported [38]. These peptides were shown to stimulate proliferation of $\gamma\delta$ T cells in BS [39]. Immune response against retinal S antigen which is normally an immunologically privileged retinal protein is shown in BS uveitis [40, 41]. Homology has been reported between retinal S antigen and HLA-B51 and HLA-B27 [42]. All these data suggest a role for *molecular mimicry* in BS pathogenesis.

In recent years the role of Th17 has gained importance in BS pathogenesis especially since high levels of IL-17, IL-23, and Th17/Th1 ratio were reported in active BS [23, 43]. As there is high frequency of mucosal lesions in BS, $\gamma\delta$ T cells, major part of mucosal immunity, have been studied in BS. Accumulation of $\gamma\delta$ T cells in inflammation sites has been reported in BS [44]. $\gamma\delta$ T cells also have been shown to be strong Th1 and Th17 inducers in experimental models [23].

15.5 Clinical Manifestations

15.5.1 Mucocutaneous Disease

The most common initial manifestation of BS in both children and adults is oral *ulcers* [10, 11, 15]. Painful unique or multiple oral ulcers appear in the tongue, pharynx, buccal, and labial mucosal membranes, and elsewhere in the gastrointestinal tract. The typical lesion is round with an erythematous border, usually $<$10 mm but larger lesions (1–3 cm) may also occur. The lesions usually heal within 10 days without scarring but in neonatal disease, extensive scarring can be seen [45]. The lesions are indistinguishable from canker sores, but their recurrence should urge to look for other manifestations of BS [46, 47].

The genital ulcers, much less common than oral ulcerations, are characterized by clear demarcation, great depth and pain. They heal and recur, leaving scar in almost half of the cases. They are mostly localized on the scrotum in men, and vulva and vagina in women [46, 47]. Genital aphthosis is rarely seen alone and usually accompanied by oral aphthosis in BS patients [48]. A recent study demonstrated that genital ulceration was significantly associated with the female gender in children [49].

Different types of skin lesions occur in more than 90 % of children with BS [46]. The most frequent skin manifestations are pseudofolliculitis and erythema nodosum like lesions [47]. But also papules, pustules, vesicles, pyoderma gangrenosa-like lesions, palpable purpura, and hypopigmented lesions have been reported [50, 51].

Pathergy, a pustular reaction induced 24–48 h after a cutaneous pitch, is one of the characteristic features of BS, but not pathognomonic [52]. Pathergy test positivity ranges between 40 and 80 % in different series, but occurs most commonly in patients along the ancient Silk Road [15]. A recent study demonstrated that without positive pathergy test as a criterion for BS diagnosis, the sensitivity of the classification criteria decreased, while the specificity improved [53].

15.5.2 Eye Disease

Ocular involvement prevalence in childhood BS was reported to be within the range of 27.3–80 % [15, 51, 54–56]. Series specifically addressing the eye involvement of childhood BS revealed a nearly twofold prevalence of males [11, 57]. A variety of eye lesions have been found including anterior uveitis, cataract, glaucoma, posterior uveitis with retinal vasculitis, vitritis, retinitis, panuveitis, retinal edema, cystoid macular degeneration, venous or arterial occlusion, disc edema, and retinal detachment [47]. Posterior uveitis is the most common ocular manifestation [56]. The disease is usually bilateral and uveitis occurs more frequently in boys than in girls [10, 56]. Conflicting reports exist in comparison of prevalence and prognosis of ocular involvement between adults and children [10, 12, 55]. Prognosis is severe as the course is characterized by frequent relapses. However, with intensive therapy and care, an improvement in visual outcome may be achieved [47].

15.5.3 Vascular Disease

BS is the only vasculitis that affects vessels of all sizes in both the arterial and *venous* systems throughout the body [58]. It affects the veins in the form of thrombosis, whereas it manifests as aneurysm, stenosis, and thrombosis of the arteries [59]. Mostly, thromboses occur in the veins of the lower extremities in adults [60]. However, in a study on pediatric BS patients with thrombosis, main location for thrombosis were the cerebral sinuses (52.4 %) [61]. Pulmonary artery thrombosis is a rare but severe feature of the disease which is associated with high morbidity and mortality rates [59, 62, 63].

15.5.4 Central Nervous System Disease

Central nervous system (CNS) involvement was estimated to occur in 11–50 % of children with BS [64], although it is relatively rare in adult patients (10 %) [65]. Unlike children, adult patients often develop neuro-Behçet after some non-neurological manifestations of BS which makes it easier to diagnose [66]. A recent study demonstrated that the mean age at presentation of neurological findings in children with BS was 11.8 years with male gender prevalence (ratio 2.9:1) [67].

Neuro-Behçet has been divided into two major forms according to the radiological pattern: (1) the parenchymal form (with acute and chronic progressive patterns) and (2) the non-parenchymal (or vascular) form [68]. In the parenchymal form, the acute pattern is characterized by acute meningoencephalitis with or without focal lesions; the chronic progressive pattern is characterized by slowly progressive central and peripheral alterations like dementia, ataxia, or dysarthria [69, 70]. In the non-parenchymal type, the pathological process is localized in the large venous or arterial cerebral vessels [71]. Among children, the vascular type is more common [72].

15.5.5 Other Manifestations

BS may affect any system or organ including joints, muscles, gastrointestinal tract, kidney, and the heart.

Joint involvement occurs in 20–80 % of children with BS [10–12, 15]. The disease is usually in the form of oligoarthritis [10, 48]. It follows a mild and transient course in most of the cases and commonly involves the large joints such as the knees, ankles, wrists, and elbows [10]. Myositis is rarely associated with BS but has been reported in children [73].

The characteristic lesions of BS in gastrointestinal system are deep penetrating ulcers mostly located in the terminal ileum, the ileocecal region, and the colon [74]. Gastrointestinal tract ulcerations are histologically indistinguishable from Crohn disease, nevertheless the granuloma formation can be used to rule out BS [47]. Gastrointestinal involvement of BS causes nausea, abdominal pain, anorexia, and diarrhea which can be bloody [47]. In a pediatric cohort of BS, gastrointestinal symptoms in the form of abdominal pain were reported in 26 % of the patients [49].

Renal involvement is rare and the most common form is amyloidosis occuring in patients as young as 13 years old [46]. Secondary effects of venous or arterial *thrombosis* have also been reported [47].

Serosal inflammation was reported in the form of pleuritis, pericarditis, and orchitis in a recent cohort of pediatric BS patients [49].

A number of cardiac complications such as angina pectoris, myocardial infarction, and pericarditis have been shown in adult cases [48] but rarely seen in children.

It has long been suggested that BS has certain clusters of disease manifestations. However, no distinct subgroups have been shown up to now [75].

15.6 Laboratory Examination

In BS, there is no diagnostic laboratory test. Leukocytosis may be encountered. The acute phase reactants are seldom elevated during the active phase of BS and are not well correlated with disease activity [47].

Several autoantibodies have been investigated in BS without any convincing result. Autoantibodies are expected to be negative [23].

BS was associated with increased levels of serum tumor necrosis factor (TNF) without an increase in cerebrospinal fluid (CSF) [76]. Increased levels of IL-6 were shown in CSF of neuro-Behçet patients compared with controls [77]. CSF analysis may also reveal a predominance of neutrophils and low glucose levels [78].

Arterial and venous thromboses are features of BS. Large studies have failed to find any difference according to a variety of prothrombotic factors (e.g., factor V Leiden, prothrombin G20210A, MTHFR C677T polymorphisms, factor VIII, and homocysteine) between BS patients with or without thrombosis [79, 80]. However, a meta-analysis have reported higher prevalence of hyperhomocysteinemia among BS patients with thrombosis [81]. The exact mechanism of thrombosis is not clear but endothelial dysfunction and neutrophilic vessel infiltrations are thought to play major roles in the thrombotic process of BS [23].

15.7 Imaging Studies

Magnetic resonance imaging (MRI), which can be combined with angiography represents the mainstay examination to evaluate neuro-Behçet patients. The most typical MRI findings appear as lesions with high signal intensity on T2-weighted sequences [47, 82, 83]. A specific study on MRI interpretation of the parenchymal form in childhood BS stated that neuro-Behçet should be suspected in patients who have brainstem and/or diencephalic lesions that extend along the long tracts whether or not the lesions are associated with periventricular and subcortical lesions [84]. Single photon emission computed tomography (SPECT) is very sensitive in detecting vascular lesions of neuro-Behçet disease in children and it may support the clinical diagnosis [67].

15.8 Diagnosis

The diagnosis of BS is based on the clinical diagnostic criteria defined by the International Study Group in 1990 [2]. However, BS diagnosis is challenging because major manifestations emerge at different time points throughout the disease course. The patient usually presents with aphthous stomatitis as the initial sign and other components of BS may not appear for years. In addition to this, these criteria are validated in adults and do not address the differences that exist in childhood BS cases. Common differences of childhood BS cases are a higher rate

of family history, more neurologic and gastrointestinal involvement, and less prevalent occurence of genital ulcers [13, 15].

The differential diagnosis includes a variety of diseases depending on the site of involvement.

15.9 Treatment

BS is difficult to treat and we lack controlled multicenter studies for treatment of childhood BS. In 2008, the European League Against Rheumatism (EULAR) recommendations were proposed for BS management [74]. We mainly depend on this guideline which is based on adult experience and not specifically developed for the treatment of childhood BS. Therapy in BS depends largely on the site and severity of involvement and has to be tailored to the individual patient.

15.9.1 Oral and Genital Ulcers

The first line treatment for oral and genital ulcers is suggested to be *topical* only (sucralfate or steroids) [74]. Colchicine has beneficial effects on the mucocutaneous symptoms decreasing the number, size, and recurrence of aphthous lesions [85]. It should be preferred when the dominant lesion is erythema nodosum [74]. *Thalidomide* is also very effective for severe mucosal ulcerations [86]. Contraception is mandatory in women of childbearing age as it is a potent teratogen. Peripheral neuropathy is another limiting side effect of this drug [86].

15.9.2 Eye Disease

The recommended initial treatment for inflammatory eye disease in BS is azothiopurine (AZT). If the inflammation affects the posterior segment, then a combination of AZT and systemic corticosteroids should be preferred. The addition of cyclosporine and infliximab is recommended in patients with severe loss of visual acuity, retinal vasculitis, or macular involvement [74]. Topical steroids are widely used during acute episodes but there is no strong evidence for their efficacy [74].

15.9.3 CNS Disease

There are no controlled data for management of CNS involvement in BS. For parenchymal involvement, suggested agents include corticosteroids, interferon alpha (IFNα), AZT, cyclophosphamide, methotrexate, and anti-TNF drugs. Corticosteroids are recommended for dural sinus thrombosis [74]. Multiple case reports described the use of infliximab [87], etanercept [88], and adalimumab [89] with good efficacy in refractory cases.

15.9.4 Vascular Disease

Controlled data are lacking in the literature for management of vascular disease in BS. The venous thrombosis in BS is primarily due to the inflammation of the vessel wall. For the management of acute deep vein thrombosis, agents such as corticosteroids, AZT, cyclophosphamide, or cyclosporine A are recommended. Cyclophosphamide and corticosteroids are the basis of treatment in the case of pulmonary and peripheral arterial aneurysms [74]. These agents have been used for the pediatric cases as well [59]. Interferon alpha and anti-TNF treatment have been used in resistant cases.

There is no high-level evidence for the benefit for *anticoagulation* in the management of thrombosis in BS [74]. Thus the use of anticoagulants is controversial.

15.9.5 Other Systems

There is no evidence-based treatment for gastrointestinal involvement in BS. Except for surgical emergencies, medical treatment with immunosuppresives is recommended. These immunosuppressive agents include sulfasalazine, corticosteroids, AZT, TNFα antagonists, and thalidomide in the first line [74].

Colchicine is usually effective in management of arthritis in BS. There are also case reports about the use of IFNα, AZT, and TNFα blockers in resistant cases [13, 74].

15.10 Prognosis

BS has a chronic and relapsing course. The overall *mortality* reaches to 5 % at 10 years. Male gender, arterial involvement, and a higher number of flares are independently associated with mortality [90, 91]. In a series of 65 children and adolescents, the mortality rate was 3 % [10]. Early diagnosis and treatment are crucial.

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Behçet's Disease. Differential Diagnosis

16

Maria Grazia Sabbadini and Stefano Franchini

Behçet's disease (BD) is a multisystemic disorder characterized by oral and genital mucous ulcerations and ocular disease (panuveitis and retinal vasculitis). It can also cause damage to several other organs, such as the skin, the vessels, the nervous system, the heart, the gastrointestinal tract, and the musculoskeletal system.

At present, there is no pathognomonic diagnostic test which can allow a definitive diagnosis of BD. Laboratory tests can mainly suggest the presence of systemic inflammation, which is often the case in subjects presenting with erythema nodosum, phlebitis, and arthritis. However, acute phase reactants may result normal in mucocutaneous or central nervous system involvement.

The presence of HLA-B51 antigen is highly associated with BD, its predictive value, however, is inadequate to make individual diagnostic decisions.

A similar comment can also be made on the diagnostic criteria of BD issued by the International Study Group for BD based on the international conference held in Rochester (Minnesota) in 1989 and published in 1990 [1], although they are a very useful and frequently applied diagnostic tool, have excellent specificity, but lack sensitivity [2] and thus they are not useful for reaching the diagnosis in many cases.

Therefore, the diagnosis of BD remains a clinical one: a probabilistic evaluation which implies a lengthy differential diagnosis with several heterogeneous other pathologies.

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Some of the main clinical manifestations of BD (such as uveitis, arthritis, mucous ulcerations, acneiform lesions, and even the pathergy phenomenon) are sometimes shared by the 'autoinflammatory diseases', a group of systemic conditions which include, along with the well-known familial mediterranean fever (FMF), the far rarer hyperimmunoglobulinemia D with periodic fever syndrome (MKD), the Blau syndrome; the neonatal onset multi-system inflammatory disease (NOMID), and other cryopirin-associate periodic syndromes (CAPS), the pyogenic sterile arthritis, pyoderma grangenosum and acne syndrome (PAPA), periodic fever, aphthous ulcers, pharyngitis, adenopathy (PFAPA), and the TNF receptor associated periodic syndrome (TRAPS) [3]. However, fever is seldom a prominent manifestation of BD as it is usually in the autoinflammatory diseases, and it never presents any temporal periodicity. Furthermore, unlike BD, these diseases typically present in the neonatal or childhood period, often show a clear familial pattern of inheritance, and are frequently associated with specific known genetic mutations.

Certainly more problematic is the differential diagnosis with other systemic inflammatory diseases such as Crohn's disease, the sarcoidosis, the reactive arthritis, the MAGIC syndrome (mouth and genital ulcers with inflamed cartilage), the Sweet syndrome [4], and even with other more common conditions such as the recurrent aphthous stomatitis (RAS) or other skin manifestations related to hypersensitivity.

16.1 Mucocutaneous Manifestations

Recurrent oral aphthous ulcers are a *sine qua non* feature of BD according to the International Study Group criteria. Aphthous stomatitis in BD can precede other manifestations by months or years and is not readily distinguishable from the recurrent aphthous stomatitis (RAS), a much more common condition not associated with any systemic disease, which can present in 25 % of the general population [5]. However, in comparison with BD, oral ulcers are generally 'minor' (i.e., <1 cm) in RAS, they show a lower frequency of recurrence, are usually less painful, and have a tendency to heal spontaneously in a shorter period of time (usually within 2 weeks). Furthermore RAS only rarely involves the soft palate and oropharynx. Finally, mucous lesions of RAS frequently present since infancy but progressively reduce their intensity and duration in adulthood.

Complex aphthosis is another clinical entity characterized by recurrent large oral and genital ulcers and is considered an incomplete variant of BD. Indeed, clinical features of mucous lesions, and also histologic examination and immunofluorescence are not able to differentiate complex aphthosis from BD [6].

The first differential diagnosis to be solved when approaching a patient with oral ulcers must consider the possibility of non-aphthous oral ulcers caused by repeated local minor trauma due to dental pathology or dentistry intervention. This condition represent in fact the most common cause of oral ulcers, along with RAS.

Some dermatologic diseases may cause oral ulcers. The most clinically relevant probably are lichen planus, erythema multiforme, and bullous skin diseases, such as bullous pemphigus and pemphigoid. Such diseases can be easily recognized by the presence of their typical lesions on the skin, which are not usually present in BD. The differential diagnosis of oral ulcers must also be extended to infectious causes, such as herpes simplex, syphilis, HIV, herpangina, herpetic gingivostomatitis, and hand-foot-mouth disease. Other common causes of oral ulcers that should be evaluated are drug reactions, and nutritional deficiencies (iron, vitamin B12, folic acid). Coeliac disease may cause oral ulcers even when overt gastrointestinal symptoms are lacking, hence the research for the specific serologic hallmarks of this disease should be performed in patients with oral ulcers without an evident etiology. Certain hematological conditions may also be considered in these cases, such as cyclic neutropenia, and some forms of lymphoma [7].

Several autoimmune inflammatory systemic diseases other than BD can involve the oral mucosa leading to the appearance of ulcers, sometimes with peculiar characteristic features, such as systemic lupus erythematosus, reactive arthritis, and Crohn's disease. Oral ulcers may be a part of other rare inflammatory conditions, that we have already mentioned: the sarcoidosis, the MAGIC syndrome, the Sweet's syndrome, the so-called 'autoinflammatory diseases'. In systemic lupus erythematosus oral ulcers have more irregular and slit-like appearance with respect to BD ulcers. Mucocutaneous lesions of reactive arthritis (Reiter's syndrome) may include red patches or superficial painless mucosal erosions. In Crohn's disease the oral lesion are deep fissures, and they appear as linear ulcers. However, oral ulcers may be indistinguishable clinically from BD. Thus the diagnostic work-up must be aimed to look for other typical clinical features and laboratory markers able to specifically recognize the underlying systemic disease or to differentiate it from BD [8].

Biopsy is mandatory for ulcers that persist for longer than 6 weeks in order to exclude oral cancer.

Genital ulcers are the second most commonly observed initial manifestation in BD which occur in 57–90 % of patients. They resemble oral aphthous ulcerations but are larger and deeper, have more irregular border, and frequently heal by scarring. They appear usually on the scrotum in males and on the vulva in females. The most important differential diagnosis of genital ulcers includes sexually transmitted diseases such as syphilis, herpes simplex infection, chancroid (Haemophilus ducreyi), granuloma inguinale (donovanosis, Calymmatobacterium granulomatis), lymphogranuloma venereum (Chlamidya trachomatis) [9]. Other infectious diseases that can present more rarely with genital ulcerations are tuberculosis cutis, and acquired immune deficiency syndrome [10, 11]. Also other non-infectious condition must be considered, such as drug reactions, and the same dermatologic diseases that we already considered in the differential diagnosis of oral ulcers.

Papulopustular lesions or acne-like lesions are the most common cutaneous manifestation of BD. They are morphologically similar to adolescent acne (acne vulgaris), but their distribution is more widespread, affecting face, limbs, trunk, and buttocks (while the lesions of adolescent acne are seen more frequently on the upper

part of the body) [7]. The lesions are not always hair follicle-associated and are non-sterile showing the same bacterial flora seen in acne vulgaris. They tend to present more frequently in patients with BD with arthritis. Histologic exam may show a vasculitic picture but also a context of isolated folliculitis, which is less specific [12].

The differential diagnosis between BD-papulopustular lesions and acne secondary to corticosteroid use must not be missed. Acne and pustulosis are also present in synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome, but osteitis and hyperostosis are not feature of Behçet's syndrome [13].

Erythema nodosum-like lesions are more prevalent among females BD patients. With respect to classic erythema nodosum these lesions tend to involve areas other than the lower limbs, including the upper extremities, buttocks, and less commonly face and neck. Often the inflammatory hallmarks (erythema and edema around the lesions) are more pronounced than in classic erythema nodosum and the histopathological findings differ from the typical lymphohistiocytic septal/lobular panniculitis of erythema nodosum, showing vasculitis and a subcutaneous neutrophil-predominated infiltrate. Differential diagnosis of such lesions is primarily aimed at distinguishing BD erythema nodosum-like lesions from erythema nodosum associated with sarcoidosis or Crohn's disease, mainly because these condition may also cause uveitis and arthritis, as BD does [14]. However, in sarcoidosis, erythema nodosum is associated only with the acute onset of symptoms, often associated with bilateral ankle arthritis, and does not recur during the later course of the disease.

Superficial thrombophlebitis may resemble erythema nodosum, however, they can be easily differentiated by dermal ultrasonography: erythema nodosum-like lesions are hyperechoic, while superficial thrombophlebitis appears hypoechoic [15]. Another condition that may be considered is the early phase of Buerger disease.

The tendency to show a pathergy reaction (formation of a sterile pustule or erythematous small papule in the sites of minor trauma) is evaluated by the pathergy test, which is included in the diagnostic criteria for BD. However, this test has limits (mainly due to the method used for testing, to the different prevalence of the pathergy phenomenon among populations of different ethnic origin, and to the activity of the disease at the time of testing), already illustrated in Chap. 10, which make this useful diagnostic tool not adequately reliable, if used alone, in the differential diagnosis of BD [16]. Moreover positivity to the pathergy test can be seen also in other diseases characterized by predominant neutrophilic inflammation, such as Sweet's syndrome, pyoderma gangrenosum, and PAPA syndrome [17]. Finally, it must be remembered that the pathergy test can result positive in chronic leukemia patients treated with IFN-α [18].

16.2 Articular Manifestations

Arthralgia or overt arthritis are seen in more than half of patients with BD and can represent the onset manifestation of BD. Usually they are part of a picture of oligoarthritis involving the knees, the ankles, or the wrists. Since the arthritis of

BD is remittent and non-erosive, it must be differentiated from the articular manifestations of rheumatic disease or of other forms of seronegative arthritis, such as palindromic rheumatism, reactive arthritis (Reiter's syndrome), and other seronegative spondyloarthropathies. The possible coexistence of ocular inflammation and oral ulcers in these conditions may render the differential diagnosis more difficult. Nonetheless, involvement of the sacroiliac joints or the spine is unusual in BD, and there is not any association with the presence of HLA B27 [19]. MAGIC syndrome is described as an overlap disease between recurrent polychondritis and BD. However, ocular inflammation usually involves the sclera in MAGIC syndrome, rather than the uvea, and it usually lead to damage of auricular and nasal cartilages which are not involved in BD. The presence of synovitis associated with acne and pustulosis is typical of SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis, osteitis) and the coexistence of hyperostosis and osteitis also typical of this condition, is not seen in BD.

16.3 Gastrointestinal Manifestations

Many patients with Behçet syndrome experience abdominal pain, diarrhea, bleeding, and weight loss, similarly to irritable bowel syndrome [3].

The ileocecal region is most commonly affected, with ulcerations that may penetrate or perforate. Rarely, the esophagus and stomach may have ulcerations [19].

Wireless capsule endoscopy has now revealed that ulceration may also occur in the small intestine [3].

Intestinal lesions are most common in the ileocecal region, found in 88 % of patients in one report, usually on the antimesenteric side. Involvement of the rectum or anus is rare. There may be remnants of Peyer's patches at the margins of the major ulcers with aggregates of lymphocytes resembling destroyed lymph follicles. The ulcers may be aphthous or, alternatively, deep and round with a punched-out appearance. Longitudinal ulcers are rare [19].

The most common colonoscopic findings are localized single or multiple ulcers in the ileocecal region, with only 4 % having a diffuse distribution of lesions.

Unlike ulcerative colitis, colonic BD consists of multiple aphthous ulcers with preservation of haustra and involvement primarily of the proximal colon and terminal ileum [19].

The International Study Group criteria for BD accurately distinguished between BD and Crohn's disease. However, there are some common features. Like Crohn's disease, manifests as discrete ulcers and discontinuous bowel involvement with relative sparing of the rectum. The two diseases share extraintestinal manifestations, such as uveitis and arthritis. Unlike Crohn's disease, a vasculitis of the small veins and venules with deep ulcerations characterizes BD, generally with no granulomas, no cobblestoning, and less inflammation surrounding the ulcer. However, both diseases may have chronic nonspecific inflammation with normal intervening mucosa. The intestinal wall is of normal thickness, unlike the rigid,

narrowed segments seen in Crohn's disease. Perforation is more common in BD than in Crohn's disease since the latter is characterized by intense fibrosis. Scalloping, ulceronodular patterns, and complications such as abscess formation are not observed in intestinal BD. The findings in BD are generally milder than those seen in Crohn's disease. Rarely, characteristics of Crohn's disease occur in a patient with Behçet's. This may represent two diseases that coexist in the same patient, BD with unusual characteristics (such as granulomas), or Crohn's disease with the rare occurrence of oral and genital ulcers [19].

Despite the typical findings of BD and Crohn's disease, intestinal involvements of these two diseases may mimic each other clinically, pathologically, endoscopically, and radiologically [20].

In fact, distinguishing BD with gastrointestinal ulcerations from inflammatory bowel disease with extra-enteric involvement can be difficult, unless granuloma visible in biopsy samples indicates Crohn's disease [3].

A retrospective study published in 2008 compared nine different colonoscopic parameters in 115 Behçet's patients versus 135 Crohn's patients [20]. Using univariate and multivariate analysis, and applying classification and regression tree-generated algorithms the Authors identified a simple strategy for distinguishing the two diseases by their colonscopic findings, which can be summarized as follows: (i) the presence of ulcers with a cobblestone appearance is highly suggestive for Crohn's disease; when this is not present, the shape of the ulcers is the most important feature for distinguishing BD from Crohn's disease, in fact (ii) round-shaped ulcers are an hallmark of intestinal BD, while (iii) longitudinal ulcers are typical for Crohn's disease; (iv) in those cases where the ulcer shape is not clearly defined (defined as "irregular/geographic" shape) a focal localization of the ulcers within the colon suggests intestinal BD, while a segmental or diffuse distribution of the lesions throughout the colon suggest Crohn's disease [20].

16.4 Ocular Manifestations

Ocular involvement is a major cause of BD-associated morbidity. It is characterized by explosive attacks of uveitis with a tendency to cause hypopyon. However, the most common ophthalmic manifestation is a nongranulomatous uveitis without hypopyon [21, 22]. Ocular manifestations usually follow the onset of oral and genital ulcers by a few years [23], but approximately one-third of patients will have ocular inflammation as the initial manifestation of the disease. Males are usually more frequently and more early involved [22, 23].

Intraocular inflammation associated with BD should be differentiated from other infectious or noninfectious causes. Uveitis may occur as a result of many conditions. A variety of infectious diseases including toxoplasmosis, herpesviruses, syphilis, tuberculosis, Lyme disease, cat scratch disease, and Whipple's disease must be ruled out by appropriate testing.

One of the most difficult differential diagnosis of BD is viral retinitis with anterior segment involvement. The intraocular fluids should be subjected to culture, PCR, and immunohistochemical tests for the detection of a possible viral etiology. Syphilis causes a retinitis with vitreitis rather than a strict vasculitis. The diagnosis for syphilis is confirmed by serology. A chest radiograph which is a useful screen for tuberculosis may be useful [4, 24].

Anterior uveitis and iridocyclitis in BD should also be differentiated from HLA-B27-related anterior uveitis (idiopathic anterior uveitis, ankylosing spondylitis, Reiter's syndrome), tubulointerstitial nephritis, Kawasaki disease, and sarcoidosis [4].

In HLAB27-associated uveitis may cause recurrent iridocyclitis with hypopyon, but the inflammation is typically anterior, acute, unilateral, of less than 3 months' duration, recurrent, and nongranulomatous with fibrin. In contrast, uveitis in BD is more likely to be of longer duration, bilateral, involve the posterior segment, and have a poorer visual prognosis. The hypopyon may be mobile, forming and disappearing rapidly [22].

Sarcoidosis, may have posterior bilateral pole findings similar to those in BD but is generally more indolent, in contrast to the explosive recurrent attacks of BD. Furthermore, the vasculitis seen in sarcoidosis usually is not occlusive in nature and typically involves only veins, compared with the involvement of both arteries and veins in BD [24].

Uveitis may occur in the context of a variety of inflammatory diseases, including inflammatory bowel disease, Vogt-Koyanagi-Harada syndrome, and multiple sclerosis. Other causes of uveitis are intraocular tumors, in particular, intraocular lymphoma and reactions to medications such as cidofovir and rifabutin. The differential diagnosis further includes specific ocular inflammatory conditions, including Fuchs heterochromic iridocyclitis characterized by unilateral anterior uveitis with diagnostic corneal and iris changes; the "white dot syndromes" which are characterized by round white lesions involving choroid and/or retina and pars planitis characterized by a "snow bank" of inflammatory debris on the inferior pars plana [4].

Other conditions that may mimic the ocular changes of BD include collagen vascular diseases and viral retinitis. Conjunctivitis, scleritis, episcleritis, and sicca syndrome are uncommon and should lead one to consider alternative diagnoses [3, 24].

16.5 Nervous System Involvement

Neurologic manifestations of BD (neuro-Behçet disease, NBD) are very heterogeneous, making the differential diagnosis extremely broad and difficult. Involvement of central nervous system (CNS) usually present within the first 5 years after disease-onset, but only very rarely it is part of the first manifestations at presentation of BD.

Headache is the most common symptom of NBD. It affects 70 % of patients but often it is not associated with organic or structural alterations. Indeed it is frequently a recurrent vascular-type headache similar to migrain but, unlike the classic migraine, it is usually bilateral. Headache is usually associated with the

other systemic manifestations of BD and typically it accompanies their exacerbations. However, special attention must be paid in cases of unusually painful, persistent or refractory headache, since NBD can present with cerebral hypertension secondary to central venous thrombosis (CVT), and this condition must always be kept in mind in the diagnostic approach of headache in BD [25].

A clue to this diagnosis could be prompted by the observation of papilledema and the coexistence of other manifestations of cerebral hypertension such as vomiting and cranial nerve deficit.

Subacute meningoencephalitis represents the most frequent onset condition of parenchymal CNS involvement in NBS (80 % of cases) [26]. In these cases the differential diagnosis with infectious forms of meningitis is clearly mandatory (viral, bacterial, spirochetal, mycobacterial, or fungal forms must be considered). However, isolated meningitis without parenchymal signs might only rarely be the presenting feature of NBD.

Cerebrospinal fluid analysis in the acute phase usually show inflammatory changes in most cases of NBS intra-axial involvement, with elevated neutrophil count (which are substituted by lymphocytes later on) and increased protein concentration. Glucose levels are not reduced as it is frequently the case in bacterial meningitis. Meningoencephalitis of NBD is aseptic by definition, hence culture and PCR tests are negative. Cytologic test for cancer cells is fundamental in distinguishing BD meningitis from carcinomatous meningitis. The coexistence of meningitis and uveitis may suggest other systemic diseases such sarcoidosis or the Vogt-Kayanagi-Harada syndrome. The Vogt-Koyanagi-Harada syndrome, which occurs more commonly among heavily pigmented populations such as Asians, Hispanics, Native Americans, and Indians, is a bilateral, diffuse granulomatous uveitis associated with poliosis, vitiligo, alopecia, auditory signs, meningeal irritation, and occasional encephalopathy, although it rarely causes significant focal neurologic disease [27, 28].

Parenchymal involvement of BD most often involves the brainstem, especially around the cerebral peduncles, the pons, the thalamus, and basal ganglia. Well-known magnetic resonance (MRI) findings in neuro-Behçet disease are small foci of high signal intensity on T2-weighted images (iso- or hypointense to brain parenchyma on T1-weighted images) [29]. Differential diagnoses include mainly multiple sclerosis, but also brainstem infarction and dilated perivenular spaces [30]. Some clinical manifestations of multiple sclerosis such as optic neuritis or sensitive deficits are very unusual in NBD. On the other hand, the presence of brainstem/cranial neuropathies is more common in NBD than in multiple sclerosis. Furthermore, multiple sclerosis affects more female patients while NBD is more common in males. Finally, in multiple sclerosis cerebrospinal fluid analysis show only mild inflammatory signs but detects oligoclonal bands, which are extremely uncommon in NBD, in more than 90 % of cases [31].

Atypical parenchymal NBD disease can present as a larger space-occupying lesion. Differential diagnoses include lymphoma, other types of malignant tumors, and cerebral abscess. These atypical manifestations of neuro-Behçet disease can represent a diagnostic challenge.

The characteristic MRI lesion in parenchymal neuro-Behçet syndrome is a unilateral upper brainstem lesion extending into the thalamus and basal ganglia, however, isolated large lesions involving the brainstem, the thalamus, and the basal ganglia, are sometimes difficult to differentiate from cerebral lymphomas or glioblastomas.

An acute stroke-like onset is not common in NBS and MRI lesions compatible with classical arterial territories are also not expected. Furthermore, the subjects affected by NBS are usually younger than the typical ischemic stroke patient, therefore NBS should be primarily distinguished from conditions causing juvenile stroke, such as the antiphospolipid antibody syndrome and the primary angiitis of the CNS. However, antiphospholipid antibodies are not typical of NBS, and the radiological studies usually do not support strictly arterial vasculitis as lesions seen in imaging studies are not compatible with arterial territories in general. Obviously the absence of systemic symptoms and signs in primary CNS vasculitic disorders is also helpful to differentiate these forms from NBS.

The "non-parenchymal," vascular form of NBS accounts for approximately 20 %. The majority of these cases are due to CVT involving the dural sinus and often affects young male patients. The most relevant risk factor for the development of CVT is a previous episode of venous thrombosis. However, this diagnosis may not be easy since CVT may represent the first manifestation at the onset of BD in up to 20 % of cases.

The differential diagnosis for CVT must include: head trauma, pregnancy, and postpartum, the use of oral contraceptives. With respect to these forms the BD-associated CVT is usually more indolent and often lacks focal signs [32].

Another important differential diagnosis that must be considered is represented by the possible iatrogenic effects due to some agents that can be used in the treatment of BD [33]. This is especially true in the case of neurologic toxicity due to cyclosporine, or in cases of the neurobehavioral manifestations that can be rarely caused by NBS that are not to be mistaken for corticosteroid-induced psychosis.

16.6 Cardiovascular Disease

Vascular system involvement is seen in approximately 25–30 % of patients and is the most common cause of mortality. The main pathologic process in BD is vasculitis and perivascular infiltration affecting vessels of various sizes [34].

Vascular involvement in BD is quite distinctive with respect to the other forms of vasculitis, as it predominantly affects both veins and arteries of the low pressure pulmonary system. Vascular involvement shows wide geographic variability. When it occurs, vascular involvement is frequently present at disease onset, most commonly in male patients and those with a positive pathergy test or ocular involvement [3].

The clinical presentation of thrombosis in BD is different from what is observed in ANCA-associated vasculitis and other hypercoagulable states. Superficial subcutaneous thrombophlebitis and deep vein thrombosis (DVT) are the most common thrombotic manifestations. However, despite the increased prevalence of venous thrombosis, pulmonary embolism appears to be rare. Thromboses at unusual sites are often described (such as: superior and/or inferior vena cava, the mesenteric, portal, splenic, iliac, subclavian, axillary and retinal veins and/or dural sinuses cerebral sinuses or hepatic veins), as are intracardiac thrombi [3, 35].

Superficial thrombophlebitis may resemble erythema nodosum in some patients as it can be present with tender superficial nodules, although it can be recognized by ultrasonography showing a central lumen. Venous thrombosis is considered to be at least partially secondary to the inflammatory activation of the vascular endothelium, and no consistent abnormality of coagulation has been reported [3]. Findings of chronic venous insufficiency in the lower extremities are common in BD patients from areas of high prevalence and stasis ulceration should be differentiated from vasculitic lesions and pyoderma gangrenosum [36].

Arterial aneurysm formation is much less common than thrombosis, and accounts for only 10–15 % of vascular system involvement. Arterial manifestations of the disease involve aneurysm formation and occlusions. Aneurysms have a predilection for the pulmonary arterial tree, although aneurysms of the systemic circulation also occur.

The aorta is the most commonly affected vessel. However, unlike other forms of large vessel vasculitis (such as Takayasu's arteritis) the abdominal aorta is predominantly involved, whereas the thoracic aorta and is less commonly affected and aneurysm development in the aortic branches is very rare, especially at the thoracic levels [34].

Pulmonary artery aneurysms are the most common pulmonary lesion and are absolutely typical for BD. The most common presenting symptom of a pulmonary artery aneurysm is hemoptysis. It is important to distinguish the presence of pulmonary artery aneurysm from pulmonary embolism in any patient presenting with hemoptysis and DVT, as anticoagulation could be fatal. Considering the rarity of pulmonary emboli in BD, hemoptysis should be viewed with a very high index of suspicion for this condition [36]. CT usually can show very effectively the vascular and mediastinal findings suggestive of pulmonary artery aneurysm [34].

The association of pulmonary artery aneurysms with peripheral DVT is known as Hughes–Stovin syndrome. This syndrome shares similar radiologic and histopathologic findings with BD, but neither oral nor genital ulcerous lesions are seen. Pulmonary involvement in Hughes-Stovin syndrome is indistinguishable from that of BD and Hughes-Stovin syndrome is considered by some authors as an incomplete form or a *forme fruste* of BD.

Unlike other inflammatory conditions, acceleration of atherosclerosis does not seem to be a feature of BD [34]. The occurrence of more severe disease in men and the lack of an increased risk of atherosclerosis help to define the unique vasculitis of BD [36].

Cardiac involvement occurs in less than 10 % of patients. Cardiac lesions mostly include pericarditis, endocarditis, aortic insufficiency, intracardiac thrombosis, myocardial infarction, endomyocardial fibrosis, and myocardial aneurysm. Patients with cardiac involvement are mostly male and show more arterial and venous lesions when compared with those without cardiac manifestations [3].

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Classification and Diagnosis Criteria for Behçet's Disease

17

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17.1 Introduction

Behçet's disease was described as a new disease not very long ago, in 1937, and very soon, the need for diagnosis criteria was felt. The first set of criteria was created by Curth in 1946 [1]. The presence of two symptoms from oral aphthosis (OA), genital aphthosis (GA), skin lesions (folliculitis, erythema nodosum, positive pathergy test), and ocular manifestations (uveitis, retinal vasculitis) lead to the diagnosis. Curth criteria had a high sensitivity, but a low specificity [2, 3].

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In 1969, near a quarter century later, Hewitt in France and Mason and Barnes in UK presented their own criteria [4, 5]. Two years later, in 1971, Hewitt revised his criteria [6]. In Hewitt criteria, for the first timed a system point was used: Ocular manifestations (iridocyclitis) get 40 points. OA, GA, subcutaneous nodules, recurrent phlebitis, meningeal features, and pseudo-bulbar signs, get each 30 points. Other skin and ocular lesions (except those specified before) get each 20 points. Inflammatory arthritis, psychiatric manifestations, and orchiepididymitis get each 15 points. Prolonged fever and other systemic manifestations get 10 points. A total of 100 points or more classify the patient as having BD. The sensitivity of Hewitt was very low and the specificity very high [2, 3].

Mason and Barnes [5] divided the manifestations as major (OA, GA, Skin lesions, ocular manifestations) and minor (arthritis/arthralgia, gastrointestinal manifestations, vessel thrombosis, neurological manifestations, cardiac lesions, epididymitis, family history). A patient who has 3 major or 2 major and 2 minor manifestations is classified as BD. Mason and Barnes criteria have low sensitivity and high specificity [2, 3, 7, 8].

A year later, in 1972, Japan criteria were presented [9]. They had the same major manifestations as Mason and Barnes. The presence of 3 manifestations led to the diagnosis of BD. However, in the presence of ocular manifestations one other major manifestation was enough to make the diagnosis. The sensitivity improved greatly compared to Mason and Barnes, and to Hewitt criteria, while the specificity improved greatly compared to Curth criteria. Japan criteria was revised in 1988 [10].

In 1974, Hubault and Hamza (France-Tunisia) presented their criteria [11]. It was based on major manifestations (OA, GA, Eye lesions, and positive pathergy test) and minor manifestations (pseudofolliculitis, arthritis, and phlebitis). Three major manifestations, or two major and two minor sufficed for the diagnosis of BD. The sensitivity was much lower than Japan revised criteria, while the specificity was very close [3].

In the same year, O'Duffy (USA) presented his criteria [12]. He presented 5 major manifestations as OA, GA, dermal vasculitis, ocular manifestations, and arthritis. This was the first time that arthritis was considered as a major manifestation of BD. The presence of oral or genital manifestations, plus two other major manifestations, makes the diagnosis of BD. The performance of the criteria is very close to Mason and Barnes.

In 1980, Cheng and Zhang from China presented their criteria [13]. They too proposed major and minor manifestations. Major manifestations were OA, GA, and ocular lesions. Minor manifestations were skin lesions (comprising the positive pathergy test like the Japan criteria), arthritis or arthralgia, neurological manifestations, gastrointestinal ulcers, epididymitis, pulmonary lesions, and hematuria. Two major or one major plus two minor manifestations were sufficient to make the diagnosis. Both sensitivity and specificity are good, near 94 % [3].

Dilsen from Turkey proposed his criteria in 1986 [14]. The backbone of criteria was the positive pathergy test. Major manifestations were OA, GA, skin lesions, ocular manifestations, and thrombophlebitis. Minor manifestations were arthritis

or arthralgia, gastrointestinal manifestations, arterial thrombosis, neuropsychiatric manifestations, cardiac lesions, pulmonary manifestations, epididymitis, family history of BD, and history of positive pathergy test. In the presence of positive pathergy test, one major or one minor manifestations was sufficient to make the diagnosis of BD. If pathergy was suspect, two major or one major and one minor were necessary to make the diagnosis. If pathergy was negative then three major, or two major and two minor were necessary to make the diagnosis of BD. The sensitivity of the criteria was rather low, lower but near the Japan revised criteria. The specificity was rather high, as good as Cheng and Zhang criteria [3].

17.2 International Study Group Criteria

As many countries had presented their own criteria and no consensus could attain to which one to use internationally, in 1990 the first internationally agreed criteria with the collaboration of the above countries (except China), and also the collaboration of Iran, was presented under the name of the International Study Group (ISG) criteria [15]. For ISG, the backbone was OA. More than that, its presence was mandatory. The patient could be classified as BD if two of the following manifestations were present: GA, skin manifestations, ocular lesions, and positive pathergy test. In the cohort of patients gathered from France, Iran, Japan, Tunisia, Turkey, UK, and USA, the sensitivity was 92 % and the specificity was 94.5 % [15].

17.3 Validation Studies Leading to New Criteria

The first validation study done on 1993 [7] showed lower sensitivity (86.2 %) of ISG with a higher specificity (97.5 %).This validation study was from Iran, which gave 366 of 886 patients of the ISG cohort of patients [16]. As the results were not as good as expected, the race to create better criteria continued. Iran presented two sets of diagnosis/classification criteria. One had the traditional format as the precedent criteria, named Iran criteria [7]. The second was named classification tree, using the method of the classification and regression tree analysis [17]. Iran criteria used the same elements as the ISG criteria; OA, GA, skin lesions, ophthalmologic manifestations (uveitis, retinal vasculitis), and the positive pathergy reaction. The difference with ISG was that OA was not mandatory anymore. All symptoms got 1 points each, except ophthalmological manifestations, which got 2 points. A score of 3 points or more was synonym of BD. The performance was as follow: sensitivity 90.6 % and specificity 96.8 %. The classification tree (Fig. 17.1) works as follow: In the presence of OA, if the patient has also GA, then the patient is classified as BD. If the patient has not GA, but has ocular signs, then the patient is classifies as BD. In the absence of ocular signs, if the patient has a negative pathergy test, then the patient has not BD. If the pathergy test is positive and skin manifestations exist, then the patient is classified as BD, otherwise the

patient has not BD. This is the left part of the classification tree. The right part starts with the absence of OA. If ocular manifestations also are lacking, then the patient has not BD. If ocular manifestations are present and the pathergy test is positive, the patient is classified as BD. The sensitivity improved greatly to 97.1 % and the specificity at 97.3 % [3].

Dilsen (Turkey) revised its criteria in 2000 [18]. Dilsen discarded from his criteria the minor manifestations, and gave the same value to positive pathergy test as other major manifestations. In the revised form, the presence of 3 manifestations led to the diagnosis of BD. The sensitivity of the revised form decrease slightly from the original form (2.6 %) and improved moderately the specificity (4.9 %).

In 2002 and 2003, Korea presented its own criteria [19, 20]. Korean criteria are based on system point, like the Iran criteria. GA takes 2 points and the followings each 1 point: OA, skin manifestations, ocular lesions, gastrointestinal manifestations, and the positive pathergy test. Three points or more classify the patient as having BD. The sensitivity and the specificity were the same as the Japan revised criteria. A summary of the performance of the above criteria, in Iranian patients [3], are given in Table 17.1.

From 1993 till 2004, several validation studies compared the ISG criteria to some of the frequently used criteria mentioned above [7, 21–24]. The performance of ISG regarding sensitivity was low. It ranked 5th in patients gathered from China, Iran, and Korea [21]. It ranked again 5th in Russia [22], 7th in USA [23], 7th in India [24], and 7th in Singapore [24]. The comparison was made among 7 sets of diagnosis criteria; Mason and Barnes, O'Duffy, ISG, Dilsen, Japan revised, Iran, and the classification tree.

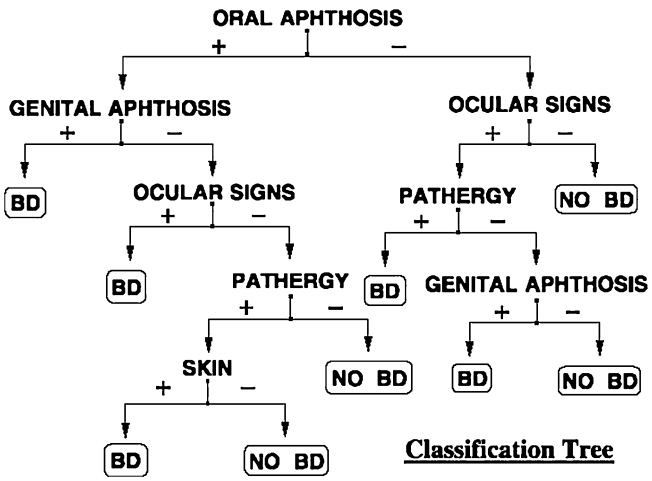

Fig. 17.1 Classification tree (Iran)

Table 17.1 Performance of classification/diagnosis criteria [3]

Criteria	Sensitivity (%)	Specificity (%)
Curth	99.7	84.4
Hewitt	37.5	99.8
Mason and Barnes	64.3	99.7
Japan	84.7	97.7
Hubault and Hamza	61.1	98.9
O'Duffy	68.8	98.4
Cheng and Zhang	93.6	93.9
Dilsen	82.2	93.8
Japan revised	85.8	97.6
ISG	78.1	98.8
Iran	90.6	96.8
Classification tree	97.1	97.3
Dilsen revised	79.6	98.7
Korea	86.4	97.9
ICBD traditional	98.2	95.6

As the above comparisons showed all a lack of performance for the ISG, and no consensus to use one of the mentioned criteria for diagnosis/classification of the disease, it was decided during the first workshop of the International Society for Behçet's Disease, held in Kuhtai, Austria, in April 2003, to revise ISG. Therefore, in 2004 during the 11th International Conference on Behçet's Disease, held in Antalya, Turkey, the International Team for the Revision of the ISG criteria was created. It was constituted by 27 countries: Austria, Azerbaijan, China, Egypt, France, Germany, Greece, India, Iran, Iraq, Israel, Italy, Japan, Jordan, Libya, Morocco, Pakistan, Portugal, Russia, Saudi Arabia, Singapore, Spain, Taiwan, Thailand, Tunisia, Turkey, and USA.

17.4 International Criteria for Behçet's Disease

From June 2004 till June 2006, a total of 3,719 patients (2,556 BD patients, 1,163 controls) were gathered from these countries. The first action was to look at the performance of the existing criteria on this internationally gathered cohort of patients [25]. Results are given in Table 17.2. As on sensitivity, the ISG criteria ranked 13 on 14 evaluated criteria, validation failed and it was decided to create two new set of criteria, one in the format of the traditional criteria, named International Criteria for Behçet's Disease (ICBD), and one on the format of classification tree criteria [26, 27].

Table 17.2 Performance of classification/diagnosis criteria in ICBD patients [25]

Criteria	Sensitivity (%)	Specificity (%)	Accuracy (%)
Curth	98.6	83.2	93.8
Hewitt	85.7	90.2	87.1
Mason and Barnes	79.3	96.1	84.6
Japan	86.2	92.4	88.2
Hubault and Hamza	82.5	91.5	85.3
O'Duffy	83.2	94.6	86.7
Cheng and Zhang	96.4	78.3	90.7
Dilsen	86.9	90.9	88.2
Japan revised	87.9	92.0	89.2
ISG	82.4	96.0	86.7
Iran	88.2	92.3	89.5
Classification tree	94.6	90.3	93.3
Dilsen revised	84.0	95.8	87.7
Korea	90.4	92.9	91.2

For the traditional format of ICBD, GA and ocular lesions were given each 2 points. OA, Skin manifestations, vascular manifestations (arterial and venous thrombosis, aneurysm), and positive pathergy test were given 1 point each [28]. Three points or more are needed to diagnose/classify the patient as having BD (Table 17.3). The sensitivity was 96.1 % with a 95 % confidence interval (95 % CI) of 95.3–96.9 %. The specificity was 88.7 % (95 % CI: 86.9–90.5 %). The accuracy (percent agreement) was 93.8 % (95 % CI: 93.0–96.6 %).

For the classification tree, eye lesion + OA, or eye lesion + vascular lesion, or eye lesion + GA, or GA + OA, or skin + OA + positive pathergy test is synonym to BD (Fig. 17.2). The sensitivity was 94.8 % (95 % CI: 94.0–95.6 %). The specificity was 91.8 % (95 % CI: 90.2–93.4 %). The accuracy was 93.9 % (95 % CI: 93.1–94.7 %). The traditional format of ICBD was validated in China in 2008 [29], in Germany in 2008 [30], and in Iran in 2010 [3]. The ICBD, both the

Table 17.3 International criteria for Behçet's disease (ICBD), traditional criteria

Oral aphthosis	1 point
Skin manifestations	1 point
Vascular lesions (arterial and venous thrombosis, aneurysm)	1 point
Pathergy positive test	1 point
Genital aphthosis	2 points
Ocular lesions	2 points

Behçet's disease: 3 or more points

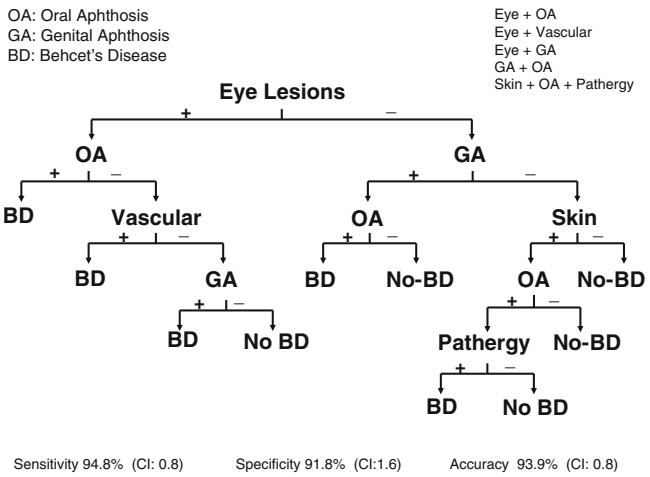

Fig. 17.2 ICBD classification tree

traditional format and the classification tree format were adopted by the 2008 Fitzpatrick's textbook of Dermatology in General Medicine [31], and by 2013 Kelley's Textbook of Rheumatology [32].

17.5 Revision of ICBD

The traditional format of ICBD was revised in 2010 and presented to the 14th International Conference on Behçet's Disease in London, and published in 2013 [33]. In the revised form of the criteria, OA gained a value of 2 points instead of one; neurological manifestations were added and given 1 point. Pathergy test became facultative in the revised ICBD. To summarize, skin manifestations, vascular lesions, neurological manifestations, and the pathergy test were given 1 point. OA, GA, and ocular manifestations were given 2 points. A patient was diagnosed or classified as BD with 4 points or more. The sensitivity of the revised criteria without the pathergy test, and in the "training data set" was 93.9, and the specificity was 92.1 %. In the "validation data set," the sensitivity was 94.8 and the specificity 90.5 %. Now, including the pathergy test, and in the training data set, the sensitivity became 98.5 % and the specificity 91.6 % if the data in those not having done the test were adjusted [33]. However, if all the data (training and validation data) are put together and no adjustment is done (regarding the pathergy test), the result will become without the pathergy test: sensitivity 94.3 % (95 % CI: 93.4–95.2), specificity 91.5 % (95 % CI: 89.9–93.1), and accuracy 93.4 % (95 % CI: 92.6–94.2). With the pathergy test, the results become sensitivity 96 % (95 % CI: 95.2–96.8), specificity 91.2 (95 % CI: 89.6–92.8), and the accuracy 94.5 % (95 % CI: 93.8–95.2). As seen by these results, the revision improved

Table 17.4 Revised ICBD, traditional criteria

Skin manifestations	1 point
Vascular lesions (arterial and venous thrombosis, aneurysm)	1 point
Neurological manifestations	1 point
Pathergy positive test	1 point
Oral aphthosis	2 points
Genital aphthosis	2 points
Ocular lesions	2 points

Behçet's disease: 4 or more points

slightly the specificity from 88.7 to 91.2 %. Although the difference is minimal (2.5 %), it is statistically significant. The sensitivity lost 0.1 % compared to the original, and the difference was not significant (Table 17.4).

Looking at the cohort of patients in Iran (7011 BD patients and 5,226 controls, data up to March 2013), the performance of different ICBD compared to ISG gives the following results for ICBD traditional, revised ICBD without the pathergy test, revised ICBD with pathergy test, classification tree, and ISG criteria. Sensitivity 98.3, 91, 96.8, 95.7 %, compared to 77.5 %. Specificity 96.2, 97.7, 97.2, 97.4 %, compared to 99.2 %. Accuracy 97.4, 93.9, 97, 96.4 %, compared to 86.7 %.

17.6 Conclusion

Many criteria sets were produced since 1946, to be exact 19 sets. Six sets have a sensitivity superior to 95 % in the large cohort of patients from Iran: Curth, classification tree (Iran), ICBD, ICBD revised (no pathergy test), ICBD revised, and ICBD classification tree. Seventeen sets have a specificity superior to 95 %. Four sets have an accuracy superior to 95 %: classification tree, ICBD, ICBD revised with pathergy test, and ICBD classification tree. As no significant difference exists between the Iran classification tree (97.3 %), ICBD (97.4 %), and the revised ICBD (97 %), it is proposed to use the revised ICBD with pathergy test.

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Prognosis and Disease Activity

18

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18.1 Prognosis

In 1990, the International Study Group (ISG) for Behçet's disease (BD) proposed the validated classification criteria; to fulfill these criteria a *conditio sine qua non* for the diagnosis had to be the presence of recurrent oral ulcers, together with two or more of the following symptoms: recurrent genital ulcerations, eye lesions, skin lesions, or a positive pathergy test [1]. However, articular, vascular, gastro-enteric, and neurological involvement may also occur. Globally, BD is characterized by a variable spectrum of disease profile: while prevalent mucocutaneous lesions and arthritis represent the only clinical feature in patients with a benign disease subset, there are other patients who potentially develop sight or life-threatening manifestations, due to ocular, neurological, or major vascular involvement [2–4].

Beside the organ involvement, a number of demographic factors could considerably influence the long-term and short-term outcomes of BD: age at disease onset, duration of disease, gender, and sex [5]. Younger men patients are more suitable to have a more severe disease, due to an increased frequency both of morbidity and mortality, related to ocular, vascular, and neurological involvement [6].

18.1.1 Ocular Involvement

Eye involvement represents one of the most serious manifestations of BD and occurs in half of the patients. It seems more frequent and severe among young males and, unluckily, it still remains one of the most significant causes of

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morbidity [7]. Usually, ocular disease develops within the first years of the disease onset and seems to be more severe in this period; moreover, growing data have suggested that the prognosis of BD patients with ocular involvement is mainly dependent upon the severity of visual acuity at presentation [8, 9]. Posterior or panuveitis associated with retinal vasculitis are the most common ocular manifestations; they can be extremely severe, causing hemorrhages, retinal exudates, venous thrombosis, papilledema, and macular disease. Structural changes, such as synechiae and retinal scars, are the consequences of its relapse course, which may lead in many patients to permanent visual impairment or blindness. The involvement of the anterior chamber with severe inflammation (hypopyon) indicates a poor outcome and is generally associated with severe retinal vasculitis. Isolated anterior uveitis is less frequent; moreover, conjunctivitis is sporadic. The anatomical classification of ocular involvement in BD has important therapeutic and prognostic implications: while attacks restricted to the anterior segment can be sufficiently managed with topical treatments, inflammation localized to the posterior segment always needs treatment with glucocorticoids and immunosuppressive therapies. Moreover, the specific site of inflammation, associated with the clinical course, represents a relevant reference point for the choice and duration of the therapy. Globally, the main determinant of visual prognosis is represented by the number of ocular attacks during the follow-up period; in this scenario, visual acuity represents the best marker of damage in ocular involvement.

18.1.2 Neurological Involvement

Although not included in the ISG criteria for BD, neurological involvement represents the second main cause of mortality, preceded by large vessel disease [6]. There have been many studies describing the prevalence of neuro-BD in different countries that varies from 2 to 50 % [10–13]. Despite immunosuppressant therapy, neurological involvement is still considered a worrying complication of the disease, representing an important cause of morbidity and mortality. Although neuro-BD may present with different neurological problems, directly or indirectly related to the systemic disease, it is usually categorized into two main groups: parenchymal brain involvement (more frequent, 80 % of cases) and nonparenchymal or vascular disease. Parenchymal CNS involvement, mainly affecting the brainstem, occurs with pyramidal signs, cerebellar symptoms, sphincter disturbance, and behavioral changes. Vascular disease is generally due to intracranial hypertension secondary to dural sinus thrombosis. Headache undoubtedly represents the most common neurological symptom observed in patients with neuro-BD, and can be associated to different etiologies (i.e., parenchymal involvement, cerebral venous sinus thrombosis, ocular inflammation, co-existing, primary headache). Moreover, it seems relatively frequent that patients with BD may develop a neurobehavioral syndrome, characterized by bipolar disorders and paranoid attitudes, called “neuro-psycho-BD”. So far, it is not clear which is the pathogenetic mechanism underlying this syndrome: it may be secondary to an organic neurological involvement or related to

the poor quality of life and the relapsing course of disease. Parenchymal CNS involvement represents a serious morbidity of disease, often leading to disability and to mortality, if not treated early. On the other hand, dural sinus thrombosis is associated with a more favorable outcome than parenchymal involvement.

Notably, the onset of CNS involvement seems to occur in the first 10 years, with a higher incidence rate in the first 5 years [11]. These data have surely important clinical implications, since the timing of onset of neuro-BD strongly affects the scheduling of the follow-up timing. Indeed, neuro-BD is still related to high rates of morbidity and mortality: early recognition of severe organ involvements could certainly represent an important element to prevent irreversible damages due to the chronic-relapsing course of the disease. As suggested in other systemic autoimmune diseases, a disease-specific set of quality assessment tools should help physicians deliver a high quality of care in neuro-BD patients [14].

18.1.3 Vascular Involvement

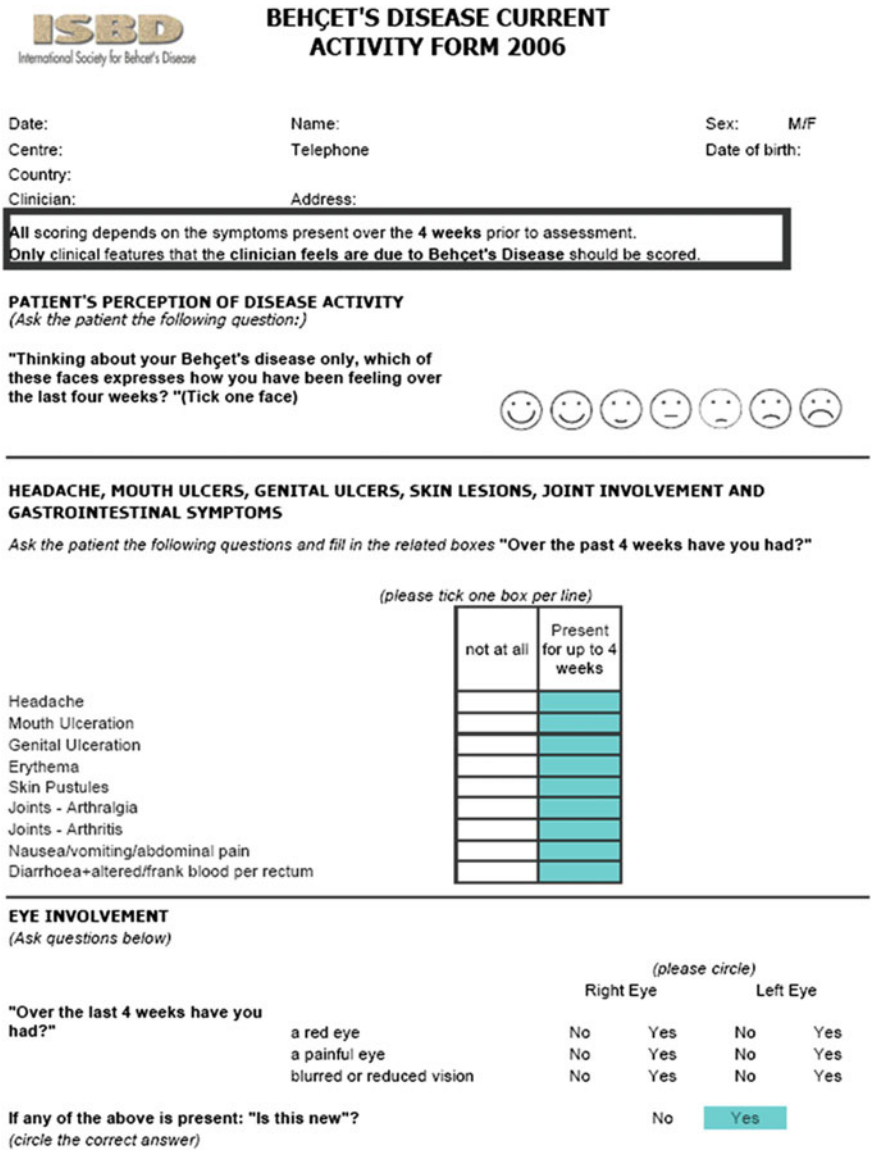
The prevalence of vascular involvement varies from 20 to 35 % of BD patients and it may involve all types of vessels within the arterial and venous system. It is characterized by a clear male preponderance. Vascular involvement in BD represents a serious risk for multiple vessel-related complications, including thromboses, stenoses, occlusions, and aneurysms. While arterial involvement is less common (3–12 %), the most common feature is represented by venous thrombosis, which mainly occurs in the lower limbs; other specific features are represented by vena cava thrombosis, pulmonary artery aneurysm (PAA), Budd-Chiari syndrome, peripheral artery aneurysms, dural sinus thrombosis, and abdominal aorta aneurysms [15–17].

The prognosis of BD patients with arterial involvement is poor, with a death rate of 13.5 % in the patients with arterial lesions, above all in presence of the pulmonary artery and thoracic aorta involvement. PAA is a well-known cause of morbidity in BD and is associated with the highest mortality rates despite an aggressive therapeutic approach [6]. The typical clinical picture of PAA is represented by haemoptysis, dyspnea, fever, chest pain, and cough. Cardiac involvement is a rare manifestation in BD and comprises pericarditis, endocarditis with valvular lesions, myocarditis, intracardiac thrombosis, endomyocardial fibrosis, coronary vasculitis, and myocardial aneurysm formation [18].

18.2 Disease Activity

Since there are no established laboratory findings to define BD and the diagnosis remains mainly dependent on the identification of the typical clinical pictures, to a certain extent, there are no optimal measures that would simplify the evaluation of the disease. Unluckily, there are no validated biomarkers that could reflect disease activity over time. More recently, a lot of attention has been focused on the effect of the disease on the general quality of life in BD patients and two specific tools have

thus been created. The Behçet's disease current activity form represents a useful tool for monitoring the disease (Fig. 18.1) [19]. The Behçet's disease-quality of life (BD-QoL) measure was created to measure the impact of BD on the patient's daily life [20]. The BD Current activity Form is completed by the physician/assessor together with the patient, while the BD-QoL is completed only by the patient.



ISBD
International Society for Behcet's Disease

BEHÇET'S DISEASE CURRENT ACTIVITY FORM 2006

Date: Name: Sex: M/F
Centre: Telephone Date of birth:
Country:
Clinician: Address:

All scoring depends on the symptoms present over the 4 weeks prior to assessment.
Only clinical features that the clinician feels are due to Behçet's Disease should be scored.

PATIENT'S PERCEPTION OF DISEASE ACTIVITY
(Ask the patient the following question:)

"Thinking about your Behçet's disease only, which of these faces expresses how you have been feeling over the last four weeks? "(Tick one face)

HEADACHE, MOUTH ULCERS, GENITAL ULCERS, SKIN LESIONS, JOINT INVOLVEMENT AND GASTROINTESTINAL SYMPTOMS

Ask the patient the following questions and fill in the related boxes **"Over the past 4 weeks have you had?"**

(please tick one box per line)

	not at all	Present for up to 4 weeks
Headache		
Mouth Ulceration		
Genital Ulceration		
Erythema		
Skin Pustules		
Joints - Arthralgia		
Joints - Arthritis		
Nausea/vomiting/abdominal pain		
Diarrhoea+altered/frank blood per rectum		

EYE INVOLVEMENT
(Ask questions below)

(please circle)

"Over the last 4 weeks have you had?"	Right Eye		Left Eye	
a red eye	No	Yes	No	Yes
a painful eye	No	Yes	No	Yes
blurred or reduced vision	No	Yes	No	Yes

If any of the above is present: "Is this new"? No Yes
(circle the correct answer)

Fig. 18.1 BD current activity form 2006

NERVOUS SYSTEM INVOLVEMENT (include intracranial vascular disease)

New Symptoms in nervous system and major vessel involvement are defined as those not previously documented or reported by the patient
(Ask questions below)

Over the last 4 weeks have you had any of the following?	*please circle*		tick if new
blackouts	No	Yes	
difficulty with speech	No	Yes	
difficulty with hearing	No	Yes	
blurring of/double vision	No	Yes	
weakness/loss of feeling of face	No	Yes	
weakness/loss of feeling of arm	No	Yes	
weakness/loss of feeling of leg	No	Yes	
memory loss	No	Yes	
loss of balance	No	Yes	

Is there any evidence of new active nervous system involvement? No Yes

MAJOR VESSEL INVOLVEMENT(exclude intracranial vascular disease)
(Ask question below)

"Over the last 4 weeks have you had any of the following?"	*please circle*		tick if new
had chest pain	No	Yes	
had breathlessness	No	Yes	
coughed up blood	No	Yes	
had pain/swelling/discolouration of the face	No	Yes	
had pain/swelling/discolouration of the arm	No	Yes	
had pain/swelling/discolouration of the leg	No	Yes	

Is there evidence of new active major vessel inflammation? No Yes

CLINICIAN'S OVERALL PERCEPTION OF DISEASE ACTIVITY

Tick one face that expresses how you feel the patient's disease has been over the last 4 weeks.

BEHÇET'S DISEASE ACTIVITY INDEX

Add up all the scores which are highlighted in blue (front page items, one tick = score of 1 on index, all other items score 'yes' = 1. You should now have a score out of 12 which is the patient's Behçet's Disease Activity Index Score.

SCORE

Patients index score	0	1	2	3	4	5	6	7	8	9	10	11	12
Transformed index score on interval scale	0	3	5	7	8	9	10	11	12	13	15	17	20

Fig. 18.1 Continued

A growing number of studies are aimed at exploring the role of a great number of biomarkers in BD, that may have a role in monitoring the disease activity and optimizing the therapeutic approach, including proteomic biomarkers, regulatory T cells and matrix metallo-proteinase. However, further and larger studies are needed to validate their role in the disease activity assessment.

18.3 Conclusion

Younger men patients affected by BD are more suitable to have a more severe disease, due to an increased frequency both of morbidity and mortality, secondary to ocular, vascular, and neurological involvement. The variable prognosis associated with different gender or age, may represent an essential and useful element to tailor the management not only to the type and severity of symptoms, but also to the epidemiological profile of BD patients.

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Old and New Treatment for Behçet's Disease

19

Fabrizio Cantini and Gerardo Di Scala

19.1 Introduction

Behçet's disease (BD) is a chronic, relapsing, systemic vasculitis of unknown cause involving veins and arteries of all sizes characterized by protean clinical manifestations. Due to the variable severity of clinical manifestations of BD, therapeutic intervention should be modulated in function of the specific clinical feature. Indeed, BD may occur with less serious clinical symptoms and signs including mucocutaneous lesions, and articular manifestations, and severe clinical features such as ocular, vascular, neurologic, gastrointestinal, urogenital, and pulmonary involvement [1].

19.2 Current Treatment Strategies

19.2.1 Topical Treatment

19.2.1.1 Old Topical Therapies

Local application of drugs is currently employed for the treatment of aphthous stomatitis including corticosteroids (CS), antimicrobials, sucralfate, anti-inflammatory agents (benzydamine, diclofenac), anesthetics and silver nitrate.

Topical CS are useful to treat the oral ulcers of BD. Topical CS such as triamcinolone acetonide (cream or spray), or dexamethasone elixir exert an anti-

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inflammatory effect, and seem to be more effective in pain reducing and healing shortening when employed in the early stage of ulcer formation. Topical CS eye drops may be also effective in mild forms of anterior uveitis of BD, and CS creams, usually in combined therapy with antimicrobials, have been successfully employed for the treatment of genital ulcers [2]. Local application of gel, drops, suspensions, or creams containing chlorhexidine, triclosan, tetracycline, minocycline, as well as sucralfate mouthwash four times/day are effective to improve the pain, to shorten the healing, and to reduce the frequency of ulcer recurrence [2].

19.2.1.2 New Topical Therapies

Pimecrolimus. Pimecrolimus, a calcineurin inhibitor widely used in dermatology for the treatment of several forms of atopic dermatitis, has been demonstrated effective in genital ulcers of BD with pain reduction and accelerated healing by recent trials [3, 4].

Amlexanox. This compound exerts an anti-allergic and anti-inflammatory agent by inhibiting the formation and release of histamine and leukotrienes from mast cells, neutrophils, and mononuclear cells. In a recent randomized controlled trial [5], amlexanox, in form of oral adhesive pellicles, resulted significantly superior to placebo in the treatment of common aphthous stomatitis and, although not specifically investigated, it has been proposed for BD [2].

19.2.2 Systemic Therapies

19.2.2.1 Old Systemic Therapies

Corticosteroids. Even in absence of controlled trials, there is a general agreement among clinicians on the efficacy of CS, at variable daily doses or in high-dose pulses, on all clinical features of BD. High-dose CS are usually employed combined with immunosuppressive drugs in the treatment of severe BD manifestations including uveitis, neuro-Behçet, angio-Behçet, and colitis, whereas at low dose CS are effective for mucocutaneous involvement such as oral aphthosis, papulo-pustolosa, and erythema nodosum. However, the well-known side effects and adverse events associated with the long-term use of CS represent an important limiting factor, and, possibly, their use would be limited to the role of symptomatic "bridge therapy" while waiting the effects of the combined immunosuppressive therapy which is usually slower.

Colchicine. Colchicine acts inhibiting the chemotactic activity of neutrophils. In two placebo-controlled studies, the drug at the doses of 0.5–2 mg/day was effective on articular features, erythema nodosum, pseudofolliculitis, and in reducing the recurrences of genital ulcers of BD [6, 7]. An enhanced efficacy of colchicine in reducing BD disease activity has been recently reported if combined with benzathine penicillin administration [8]. Colchicine side effects, chiefly gastrointestinal complaints, may limit its use.

Rebamipide. This gastro-protective drug, acting on gastric mucosal prostaglandins release, was found to significantly improve the recurrence of oral aphthae of BD in a controlled trial of 6-month duration [9]. However, the drug is not licensed for clinical use in Western countries.

Dapsone. Dapsone inhibits the chemotactic activity of neutrophils, and in a short-term, controlled trial of 20 patients with BD, was demonstrated effective on mucocutaneous features, epididymitis, but not joint manifestations of BD [10]. Of note, dapsone employment is loaded by frequent hematological side effects with evident limits to its use.

Thalidomide. This compound exerts a weak anti-tumor necrosis factor (anti-TNF) activity. There is some evidence of efficacy on mucocutaneous manifestations of BD [2], but its clinical use is quite limited due to the frequent neurological side effects and the well-known teratogenicity.

Azathioprine (AZA). AZA is a purine analog prodrug which is converted to mercaptopurine and then metabolized to an active metabolite, thioguanine. This metabolite is incorporated into ribonucleotides, thereby exerting an anti-proliferative effect on mitotically active lymphocyte populations. AZA may also have direct anti-inflammatory properties by inhibiting cytotoxic T cell and natural killer cell function, and inducing apoptosis of T cells [11]. In early 1990s, a 24-month, randomized, placebo-controlled trial of 73 patients demonstrated the efficacy of AZA at the dose of 2.5 mg/kg/day on ocular manifestations of BD with significant reduction of uveitis flares and of the occurrence of new eye inflammatory involvement [12]. The drug was also effective on BD arthritis and oral ulcer healing, but not on papulopustular lesions and on the prevention of new ulcer recurrence. The drug has some limit in its use due to the rather low tolerability. As evidenced by a recent report [13], 17 % of 3,931 patients with Crohn's disease receiving AZA had to discontinue the treatment for adverse events including myelotoxicity, nausea, gastrointestinal complaints, immunosuppression, opportunistic infections, and hepatotoxicity over a median follow up of 44 months.

Cyclophosphamide (CYC). CYC belongs to the drug class of alkylating agents and acts blocking the production of the deoxyribonucleic acid in cells. This prevents cells from dividing, leading to cell death. Some of the cells affected by CYC are immune cells, thus explaining its use in autoimmune diseases such as rheumatoid arthritis, lupus, scleroderma, or vasculitis. There are no published controlled trials demonstrating the efficacy of CYC in BD patients. In 24-month, head to head trial of comparison with cyclosporine, no significant reduction of ocular attacks and improvement of visual acuity was observed in CYC treatment arm [14]. However, the study was carried out on only 11 patients with an obvious limitation to its consequent evidence. Nevertheless, the drug is currently employed (as monthly 1 g intravenous boluses, or 1.5–2.5 mg/kg/day, orally) to treat the more severe manifestations of BD, such as eye and central nervous system involvement. The severe safety profile of CYC characterized by myelotoxicity frequently leading to leukopenia, pulmonary fibrosis, renal toxicity, hemorrhagic cystitis, infertility, malignancy, and alopecia, suggest that the drug should be considered for use in patients with severe disease who are refractory to other agents [2].

Chlorambucil. Chlorambucil, at the dose of 0.1–0.2 mg/kg/day orally, is another alkylating agent which has been demonstrated effective in patients with BD and severe eye involvement [15]. The frequency of chlorambucil-associated side effects and toxicity such as bone marrow suppression, seizures, tremors or shaking, severe vomiting, and diarrhea limit its use in selected BD patients not responding to other traditional or more recent therapies.

Cyclosporin A (CsA). CsA is a lipophilic cyclic peptide that binds with high affinity to its cytoplasmic receptor protein cyclophilin. This complex specifically and competitively binds to and inhibits calcineurin, a calcium and calmodulin dependent phosphatase. This prevents translocation of a family of transcription factors, nuclear factor activated T cells (NF-AT), which reduces activation of genes for interleukin (IL)-2, IL-3, IL-4, granulocyte macrophage colony-stimulating factor, tumor necrosis factor alpha and interferon gamma. T-cell transcription factors AP-1 and NF-kB are also inhibited. CsA acts predominantly on CD4 cells. Consequently, CsA diminishes cytokine production and exerts an antiproliferative effect on lymphocytes [16]. The efficacy of CsA in the treatment of BD, with particular attention to uveitis, has been reported in one controlled trial [17]. CsA, at the high dose of 10 mg/Kg/day, was superior to colchicine in reducing the frequency of ocular attacks in 96 patients with BD, and was also effective on mucocutaneous features of the disease. Although with conflicting results, several open-label prospective trials have confirmed the usefulness of CsA in the treatment of different BD manifestations including hearing loss, thrombophlebitis, and joint symptoms [14, 18, 19]. CsA is not effective in neuro-Behçet, and a more frequent involvement of central nervous system has been reported in BD patients taking CsA compared to other therapies [20]. Important long-term adverse effects such as renal failure, hypertension, neurologic toxicity, and hirsutism suggest to use CsA only in more severe cases of BD, and in particular for the treatment of uveoretinitis.

Methotrexate (MTX). Although a few open-label trials reported the efficacy of MTX in neurological involvement [21], to date, the drug is prevalently employed in association with tumor necrosis factor inhibitors to treat the most severe cases of BD.

19.2.2.2 New Systemic Therapies

Mycophenolate mofetil (MMF). MMF is a prodrug of mycophenolic acid, which exerts its immunosuppressive action by inhibiting the inosine monophosphate dehydrogenase, which is the rate-limiting enzyme in de novo synthesis of guanosine nucleotides of T- and B-lymphocytes. MMF is a 5-fold more potent inhibitor of the type II isoform of inosine monophosphate dehydrogenase expressed in activated lymphocytes with consequent cytostatic effect [22]. The drug is usually employed at the dose of 1 g twice a day, orally. The efficacy of MMF in the treatment of non-infectious uveitis has been proven by several studies from ophthalmology settings. In a recently published cohort of 236 patients, 93 % of 94 patients with posterior uveitis achieved a complete remission after 6 and 12 months of MMF therapy [23]. Unfortunately, in the paper it is not reported

whether BD patients were included in this group. Similarly, in a recent Italian study, cystoid macular edema secondary to non-infectious uveitis resolved in 18 out of 19 patients [24]. MMF has been also reported as effective in the long-term treatment of neuro-Behçet [25]. If the drug is effective on mucocutaneous manifestations of BD is still unclear. Some reserves to MMF use may be related to its safety profile and tolerability with a rate of drug discontinuation of around 15 % of the patients because of gastrointestinal complaints, bone marrow suppression, elevate liver enzymes, allergy [23]. However, MMF may represent an emergent therapy for ocular manifestation of BD, and controlled trials should be performed to confirm its use as a good therapeutic option in clinical practice.

*Interferon-α (*IFN)-α. IFN-α, in addition to its powerful antiviral activity, play a critical role in modulating the Th1 immune responses via up-regulation of the high-affinity interleukin-12 beta1/beta2, and represents a pivotal cytokine responsible for the amplification of the CD8 + T cell response [26]. Over the past 10 years, a consistent body of evidence of efficacy of (IFN)-α in the treatment of BD has been provided by several trials. A randomized, double-blind, placebo-controlled study demonstrated that IFN-α 2a is effective on the mucocutaneous lesions of BD, with a significant decrease of the frequency, duration and pain of oral and genital ulcers and pseudofolliculitis. A trend to reduction of erythema nodosum, thrombophlebitis and arthritis frequency also resulted from this trial [27]. Promising results were obtained by IFN-α use inBD sight-threatening refractory uveitis. In an open-label trial of 50 patients [28] IFN-α 2a, at a dose of 6 million IU (MIU) daily, a response rate of 92 % was observed at week 52, with a significant improvement of visual acuity and remission of extraocular manifestations, with the exception of oral ulcers. Similar findings were observed in an additional study of 44 BD patients with refractory uveitis [29]. Moreover, the long-term efficacy and safety of low-dose therapy of IFN-α 2a (3.0 MIU daily for 14 days, maintenance dose, 3 MIU three times per week for 24 months) was confirmed in 37 patients with BD and refractory pan-uveitis [30]. Multiple side effects are associated with IFN-α therapy including flu like symptoms, such as fever, chills, headache, fatigue, myalgia, that start a few hours after the initiation of the therapy and continue for at least 1 day. Acetaminophen (paracetamol) 1,000 mg orally, before injections and 500 mg after 6 h during the first weeks of the therapy, is of value to reduce these side effects. Psychiatric side effects and depression, nausea, vomiting, anorexia, diarrhea, loss of weight, hematologic changes, and transient raising of hepatic transaminases may constitute additional limiting factors for use of IFN-α. Efficacy data of IFN-α 2a on the other major clinical features of BD including neuro-Behçet, entero-Behçet, and angio-Behçet are not yet available. However, IFN-α 2a represents a valid therapeutic alternative in patients with severe uveitis of BD.

Anti-tumor necrosis factor-α agents (anti-TNF). In animal models, TNF-α plays a key role in the pathogenesis of ocular inflammation [31], and serum and intra-ocular-increased concentrations of TNF-α have been detected in patients with active BD [32]. Due to this evidence, some BD patients with refractory posterior uveitis have been treated with at least four infusions of infliximab (IFX), a

chimeric monoclonal anti- TNF-α antibody at the dose of 5 mg/kg at weeks 0, 2, 6, and every 8 weeks afterwards [33–36]. All patients experienced a rapid remission of ocular inflammation over a few days. Over the following years, additional studies confirmed the efficacy of IFX in ocular manifestations of BD. Two consecutive Italian studies on 12 and 50 patients with refractory uveoretinitis, respectively, revealed a complete remission of ocular inflammatory involvement in 75 % of the cases, with a significant improvement of visual acuity [37, 38]. A similar response rate has been recently reported in a Japanese study of 50 patients [39]. In all previously quoted studies, IFX was also effective on the other manifestations of BD, and recently IFX efficacy was reported in 9 out of 10 patients with severe entero-Behçet [40], as well as in neuro-Behçet [41].

Recently, in keeping with previous case reports, adalimumab, a fully human anti-TNF-α antibody, given at the dose of 40 mg/every other week, has also been reported to be effective in all clinical features of BD in an open-label trial of 19 patients [42], and the soluble receptor anti-TNF etanercept (ETN) resulted effective for the treatment of mucocutaneous manifestations of BD in a double-blind, placebo-controlled study of 40 male patients [43]. However, the use of ETN in BD seems to be limited by its lack of efficacy on ocular inflammation as observed in anterior uveitis of ankylosing spondylitis [44]. In all studies, anti-TNF demonstrated a good safety profile.

In summary, there is an increasing evidence of the efficacy and safety of monoclonal anti-TNF for the treatment of all severe manifestations of BD, and for this reason IFX has obtained the approval for BD therapy by the Japanese Health Authorities. However, the high cost raises some concerns to promote anti-TNF as the first-line choice for the management of BD.

Rituximab (RTX). RTX, an anti-CD20 + monoclonal antibody, administered at the dose of 1 g/intravenously repeated at 2-week interval every 6 months has been recently found as an effective therapy in a pilot study of 20 BD patients with severe ocular involvement [45]. Over the last year, we also treated four patients with refractory BD uveitis and one with severe entero-Behçet. None of the patients with uveitis was responsive, while the patient with colitis achieved a complete remission (personal unpublished data). Hence, further trials on a larger number of patients are required to confirm these findings.

Tocilizumab (TCZ). TCZ is a recombinant, humanized, monoclonal, anti-interleukin (IL)-6 receptor antibody competing for both the membrane-bound and soluble forms of human IL-6 receptor with inhibition of the binding of IL-6 to its receptors and its pro-inflammatory activity [46]. IL-6 may play a pathogenic role in BD, and recently elevated cerebrospinal fluid IL-6 levels were detected in active neuro-Behçet [47]. To date, TCZ has been successfully used for the treatment of three patients with refractory BD, two of whom with neuro-Behçet [48–50]. Despite these encouraging reports, clinical trials on larger number of patients are required to confirm the efficacy of TCZ in BD.

19.3 Future Therapeutic Perspectives

Since new pathogenic pathways have been found to play an important role in BD, new biological agents targeted to IL-12/23 and IL-1β are currently under investigation. Recently, in a phase II study, all seven patients with BD and refractory ocular involvement receiving gevokizumab, a monoclonal antibody targeted to IL-1β, achieved a rapid complete remission [51]. These promising results should be confirmed in phase III trials on a larger number of subjects.

19.4 Treatment of Different Manifestations of BD in Clinical Practice

Based on the available evidence of efficacy [52], the therapeutic intervention of BD should be modulated by the different severity of the manifestations.

Mucocutaneous manifestations. Colchicine is preferable for the treatment of genital ulcers and erythema nodosum, and can be combined with benzathine penicillin [6–8]. Oral ulcers are usually more resistant, and often a short-term of combined CS therapy is required. In patients with particularly resistant mucocutaneous manifestations AZA [12], or dapsone [10] may be an effective choice, while thalidomide, due to its low tolerability profile, should be preserved as the last choice. An attempt can be also made with pentoxifylline [49]. In case of nonresponse, CsA may ensure a good result [17], otherwise anti-TNF [37, 39] or IFN-α 2a [28] should be used. Previously mentioned topical therapies should be added for oral or genital ulcers.

Articular manifestations. BD arthritis is usually mild and often self-limiting. Colchicine, preferably associated with non-steroidal anti-inflammatory drugs, and intra-articular CS represent the first choice [6]. Rarely, a low-dose, short-term CS course is needed.

Ocular manifestations. Eye involvement in BD should be regarded as a serious manifestation and requires an aggressive therapy. Anterior uveitis usually responds to topical CS drops, mydriatics or cycloplegic agents, but in case of resistance systemic CS should be added until the remission. Posterior uveitis needs high dose CS (prednisone 1 mg/kg/day or equivalent) with weekly 5 mg tapering [2, 52]. If flare occurs, an immunosuppressive drug such as CsA or AZA should be started [12, 17]. If no response is obtained, IFN-α 2a or monoclonal anti-TNF allows to achieve the remission in most cases [28, 37, 39]. MMF, CyC, and eventually RTX, due to the scanty evidence of efficacy and the low tolerability should be postponed as the last choice in unresponsive patients [14, 23].

Vascular manifestations. In our experience, CsA 5 m/kg/day combined with CS at low dose (prednisone 12.5–25 mg/day with rapid tapering) is an effective therapy for deep vein thrombophlebitis, with a good resolution of venous occlusion over a few days and avoidance of post-phlebitic syndrome [19]. In alternative, AZA can be used [2]. CYC monthly boluses should be employed in patients with

Budd-Chiari syndrome or thrombophlebitis of vena cava [2, 52]. The therapeutic role of anticoagulants or anti-platelets is still debated [53], but these drugs should be avoided in the case of pulmonary arterial aneurysm for the risk of bleeding. In arterial involvement, CS together with cyclophosphamide represents the first choice, followed by IFX in case of failure [2].

Neurologic manifestations. When central nervous system is involved, an aggressive therapy with high-dose CS (prednisone 1 mg/kg/day or methylprednisolone 1 g boluses for 3–5 consecutive days followed by oral CS) should be promptly initiated [2, 49]. In resistant cases, we suggest to employ IFX 5 mg/kg as second-line choice. Combined MTX in these cases may be helpful [21]. Due to its lower tolerability, CYC should be reserved as third-line option. Finally, in patients who are refractory to all previous therapies, TCZ may be tried [49, 50]. Anticoagulants are recommended in presence of deep sinus thrombosis [2, 52].

Gastrointestinal manifestations. CS combined with sulphasalazine is suggested as first-line choice [2, 49]. In unresponsive, IFX should be started.

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Surgical Treatment of Angio-Behçet

20

Stefano Camparini and Genadi Genadiev

Angio-Behçet patients are at risk for multiple vessel-related complications including thromboses, stenoses, occlusions, and aneurysms. Venous involvement is predominant in comparison with arterial involvement (4:1) [11]. Arterial lesions, however, pose a greater risk and are associated with a big impact on the prognosis due to the severity of complications [30]. Unique characteristics of the underlying disease process are the abating disease course and the absence of accelerated atherosclerosis. Recurrent vascular episodes are quite common with incidence of up to 23 % after 2 years and up to 40 % at 5 years [22]. Calamia et al. have proposed a classification of the vascular lesions of the great vessels (Table 20.1) [6].

20.1 Venous Involvement

Superficial thrombophlebitis (SVT) has been found by some to be the dominant lesion (up to 53 % of the patients) whereas others have found deep vein thrombosis to be more prevalent (up to 80 %) although still highly correlating with SVT [10, 21, 31]. The preferred diagnostic modality in case of peripheral vein thrombosis is duplex ultrasound (DUS) which shows incompressibility of the interested vein segment and the absence of flow on color doppler. The echogenic characteristics of the thrombus itself can help differentiate between a recent and old episode with the thrombus being hypoechoic in the former and more hyperechoic associated with wall thickening in the latter. Partial or complete recanalization can also be a finding. Duplex ultrasound is useful also in establishing the proximal

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Table 20.1 Classification of the vascular lesions of the great vessels

Systemic arterial vasculitis	
	Aneurysms
	Stenoses/occlusions
Pulmonary arterial vasculitis	
	Aneurysms
	Stenoses/occusions
Venous occlusions	
	Superficial venous thrombosis
	Deep venous thrombosis
	Cerebral venous thrombosis
	Budd-Chiari syndrome
	Portal vein thrombosis
	Right ventricular thrombosis
	Pulmonary emboli
Varices	

extension of the thrombosis and 7 the sometimes the floating nature of the head of the thrombus.

There is considerable debate as to the use of anticoagulants, antiplatelet, or fibrinolytic agents with the EULAR being against based on the notion that the thrombus usually adheres firmly to the vessel wall and does not result in emboli which would explain the low incidence of pulmonary embolism [16]. Another reason against anticoagulation could be the concomitant possibility that pulmonary artery aneurysms are present with a high risk of bleeding. On the other hand the presence of thrombophilic states in Behçet could make it imprudent to withhold anticoagulation unless a high-risk concomitant pathology like an aneurysm is also present. In addition deep venous thrombosis (DVT) episodes could precede systemic inflammation signs by months or years which questions the postulate of a highly adhesive thrombus that will not embolize [28].

Superior vena cava thrombosis can be observed in about 2.5 % of the cases and can be primary or secondary to axillary or subclavian thrombosis [7]. Plain chest radiogram can show widened superior mediastinum with collateral venous circulation. Chest CT is the definitive modality but MRI has increased sensitivity in establishing the thrombus extension particularly towards the heart. A superior vena cava syndrome can also be a result of lumen reduction due to thickening of the vessel wall without evidence of thrombosis.

Inferior vena cava (IVC) thrombosis can be caused by thrombus propagation from lower limb DVT or by in situ formation and can be found in up to a third of the patients with vasculo-Behçet [7, 10](Figs. 20.1, 20.2 and 20.3). Budd-Chiari

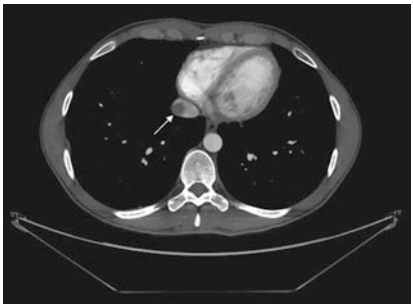

Fig. 20.1 Inferior vena cava thrombosis in its supradiaphragmatic portion right before it enters the right atrium in a 20-yr old Behçet male patient

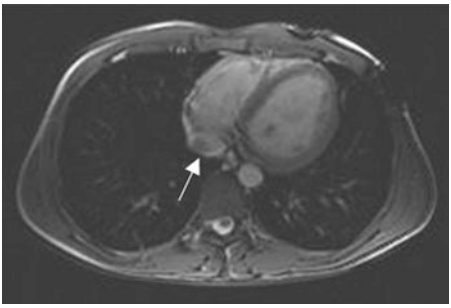

Fig. 20.2 The same lesion as in Fig. 20.1 on a Gd-DPTA MRI scan

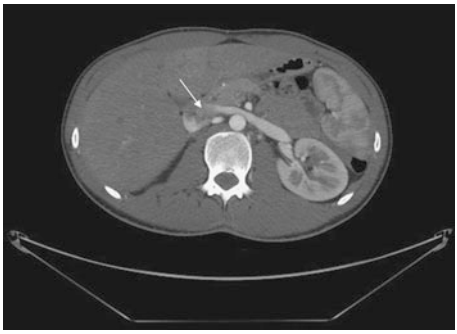

Fig. 20.3 Inferior vena cava thrombosis presenting as a filling defect during the venous phase of a Angio-CT scan

syndrome is a complication resulting from the thrombosis of the retrohepatic portion of the IVC. It can be associated with thrombosis of the hepatic veins although the latter can also occur separately. The condition leads to severe centrilobular fibrosis with an increased risk of hepatocellular carcinoma. The syndrome can be diagnosed through DUS. Direct signs include dilatation of the hepatic veins filled with echogenic content in the acute phase or thin and not visualized at all in the advanced stage. Disturbances of hepatic venous flow presenting as demodulated, monophasic, or inverted are indirect signs as well as hepatic modifications such as dysmorphic features and macronodular aspect of the parenchyma. Intrahepatic collateral flow may be observed. Both CT and MRI can help further define the diagnosis especially as asymmetry in hepatic perfusion [17].

Portal vein thrombosis is another common finding in Behçet's syndrome occurring in approximately 9.2 % of the patients and rapidly giving way to cavernous transformation characterized by numerous collaterals at the hepatic hilum and around the thrombosed portal branches [3, 7, 8]. Additional signs of portal vein thromboses are ascites, splenomegaly, hepatomegaly, and hepatic infarction. Mesenteric ischemic involvement can also lead to infectious portal vein thromboses and liver abscesses .

Surgical treatment in venous thrombosis is limited to portocaval shunting in Budd-Chiari syndrome. Transjugular intrahepatic portocaval shunt (TIPS) can be performed if the vena cava is patent. Thrombolytic therapy can be considered in the acute phase involving the vena cava or portal vein with direct infusion of urokinase or tissue plasminogen activator (tPA).

20.2 Systemic Arterial Vasculitis

Aneurysms are a more common manifestation of Behçet than arterial occlusions. The most frequent site of aneurysm formation is the abdominal aorta where a defect in the posterior wall of a usually normal aorta develops into a pseudoaneurysm rapidly progressing into rupture with shock and retroperitoneal hematoma. Theoretically, though, any artery can be involved including the visceral arteries like the splenic and mesenteric arteries.

Preferred diagnostic modalities in the case of arterial involvement are DUS and Angio-CT scanning [17]. A particular characteristic of Behçet is frequent aneurysm formation at puncture sites thus angiography should be undertaken only after careful consideration.

Immunosuppressive and corticosteroid therapy is recommended in all cases of arterial manifestations [2, 16] (Figs. 20.4, 20.5 and 20.6). An important consideration to make is that invasive treatments should not be performed in the acute and active phases of the disease when inflammation is at its peak. Surgery carries a high risk of mortality and is often unsuccessful resulting in graft occlusions, paraanastomotic aneurysms, and recurrence [16, 18]. Endovascular treatment offers some potential benefits in that regard with less postoperative complications, reduced requirements for intensive care and faster recovery times while at the same time offering comparable patency [20, 25]. Extracranial carotid aneurysms have been treated with graft interposition [4, 29], endovascular stenting [26], endovascular coil [1], or ligation [14]. Aneurysms limited to the extremities could be ligated without disabling ischemia [13, 34] (Figs. 20.7, 20.8, 20.9 and 20.10).

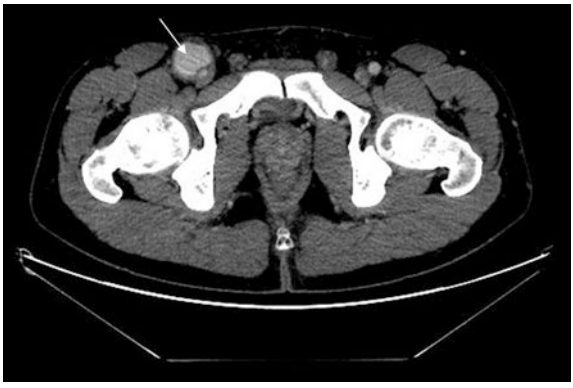

Fig. 20.4 Femoral artery pseudoaneurysm in a 36-yr old Behçet patient

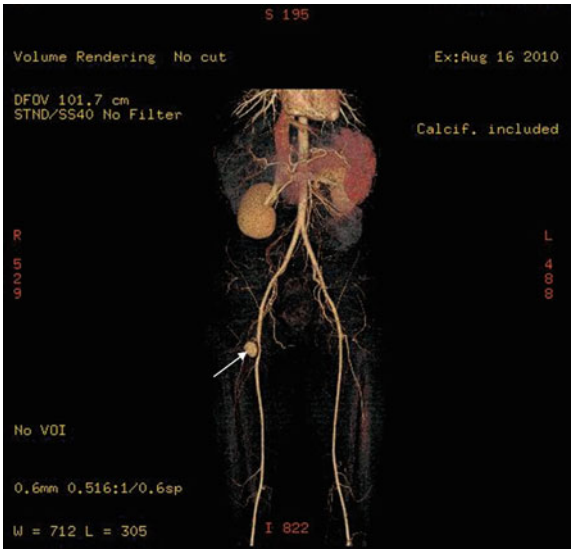

Fig. 20.5 Volume rendering of the same lesion

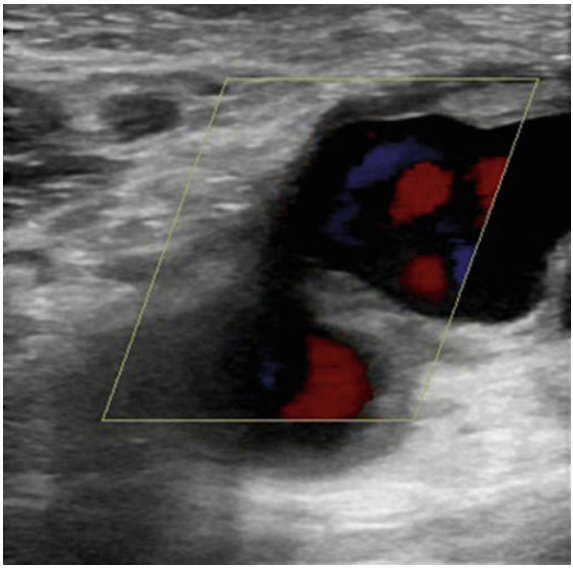

Fig. 20.6 Duplex ultrasound image of the same lesion

Arterial occlusions or stenoses may be asymptomatic or associated with ischemic symptoms, depending on the adequacy of the collateral circulation. One study has found preferred distal run-off vessel involvement whose smaller lumen is more susceptible to obliteration during the active stages of vasculitic inflammation [21]. In case a surgical treatment option is required strict follow-up protocol should be observed especially due to the tendency for anastomotic pseudoaneurysm formation regardless of the choice of synthetic or biological graft material.

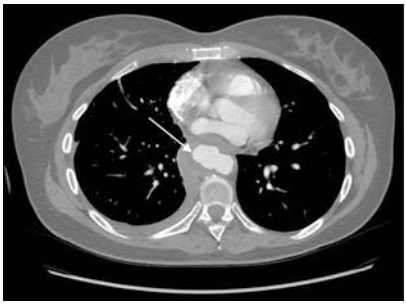

Fig. 20.7 CT scan in a 36yr old female patient presenting with a descending thoracic aorta pseudoaneyrism

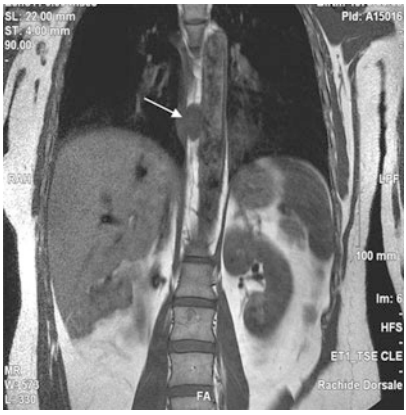

Fig. 20.8 MRI scan of the lesion

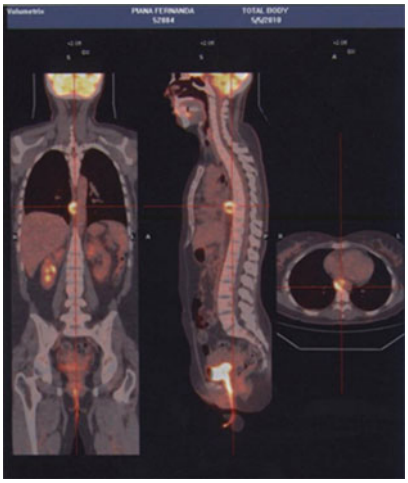

Fig. 20.9 PET scan of the lesion

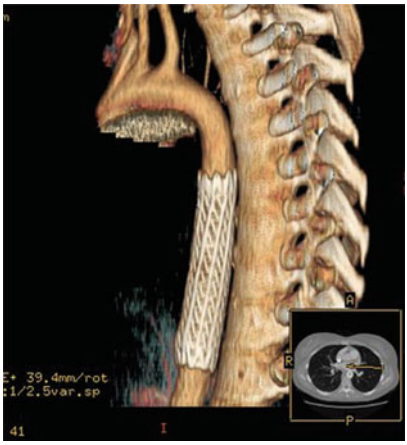

Fig. 20.10 Exclusion of the pseudoaneurysm with an endograft

20.3 Pulmonary Vasculitis

Pulmonary artery aneurysms (PAA) constitute a leading cause of death in Behçet's disease with mortality greater than 50 % [15]. Sudden uni- or bilateral hilar enlargement or the appearance of polylobular, or round opacities on plain chest radiograph are highly suspicious findings for PAA in patients known to be suffering from Behçet [32]. Angiography constitutes the gold standard in imaging but due to the risks of access-site pseudoaneurysm formations less invasive methodologies such as CT and MRI are to be recommended. Spiral CT is especially

valuable in the evaluation of pulmonary problems [35]. Emergency surgery for aneurysm rupture carries high risk and uncertain results [12, 33]. Transcatether embolization has been successfully performed in a few reports providing good outcomes at follow-up [5, 24].

20.4 Cardiac Manifestations

Although the frequency of cardiac involvement in Angio-Behçet is low it can lead to serious consequences. Coronary artery disease (CAD) is rare and is more common in male younger than 40 years old. In young patients myocardial infarction is often associated with non-atherosclerotic abnormalities such as spasm, embolization, arteritis, dissection and trauma. Coronary angiography is the gold standard for diagnosis of coronary artery syndromes but MRI and CT can also be useful. The incidence of coronary artery aneurysm is 1.5 % to 5 %. Repair of symptomatic coronary aneurysms is appropriate but avoiding bypass procedures may be best to prevent anastomotic aneurysms unless stenotic lesions are also present [19, 27]. Free grafts rather than mammary implantation might avoid later problems if the subclavian becomes involved [9].

Most of the aneurysm of the sinus Valsalva has been found in right coronary sinus which project into the right atrium or ventricle. These lesions have a high tendency for growth during the active inflammatory phase and are at a high risk of rupture. Trans-esophageal echocardiography is particularly useful in the diagnosis whereas MRI and cine-MRI can help demonstrate rupture [8]. Heart failure due to ruptured aneurysm requires urgent surgical repair.

Endomyocardial fibrosis is a rare manifestation predominantly involving the right ventricle. Occasionally it can be associated with intraventricular thrombus. Diagnostic imaging could show intraventricular filling defect with or without calcification, bright echo at echocardiography or low CT attenuation, mitral valve abnormalities, and right atrial enlargement [8]. Surgery is often required with endocardiectomy and valve replacement. Intracardiac thrombus can be treated with thrombolysis [23].

20.5 Neurovascular Manifestations

Vessel-related lesions in central nervous system (CNS) include thrombosis, aneurysms, and frank vasculitis. Cerebral venous thrombosis (CVT) is a serious manifestation commonly involving the superior sagittal sinus. CT is not usually very contributory to the diagnosis of CVT but MRI and MR venography are the excellent methods of exploration [17].

The occurrence of intracranial aneurysm in BD is very rare with the middle cerebral artery as the most common affected site. The usual presentation is subarachnoid hemorrhage secondary to aneurysm rupture. Association of extracranial

and intracranial aneurysm and multiplicity of aneurysms are reported which warrants thorough diagnostic investigation in any patient presenting with an aneurysm at a particular site. Although surgery is the first-choice treatment for ruptured aneurysms, steroid therapy may be effective for treating unruptured aneurysms in patients with Behçet disease. Conventional arteriography remains useful if an endovascular treatment (angioplasty and embolization) is considered [17].

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Index

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