Behçet syndrome: a contemporary view

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Abstract | The presence of symptom clusters, regional differences in disease expression and similarities with, for example, Crohn's disease suggest multiple pathological pathways are involved in Behçet syndrome. These features also make formulating disease criteria difficult. Genetic studies have identified *HLA-B*51* to be the important genetic risk factor. However, the low prevalence of *HLA-B*51* in many patients with *bone fide* disease, especially in non-endemic regions, suggests other factors must also be operative in Behçet syndrome. This consideration is also true for the newly proposed 'MHC-I-opathy' concept. Despite lacking a clear aetiological mechanism and definition, management of manifestations that include major vascular disease (such as Budd–Chiari syndrome and pulmonary artery involvement), eye disease and central nervous system involvement has improved with the help of new technology. Furthermore, even with our incomplete understanding of disease mechanisms, the prognoses of patients with Behçet syndrome, including those with eye disease, continue to improve.

Although Behçet syndrome is increasingly being recognized, investigated and effectively managed, its aetiology remains unclear. Indeed, the difficulty in developing universal classification criteria stems from the geographical variation in prevalence and disease expression in addition to the accumulating evidence that Behçet syndrome has several clinical subsets. Paradoxically, the more we learn, the more difficult our task of understanding Behçet syndrome becomes. Perhaps for this very reason, we prefer, contrary to the prevailing view, to refer to Behçet's as a syndrome rather than a disease. Here, we discuss the emerging, most-recent evidence on the aetiology, manifestations and epidemiology of this syndrome. We also include updated information on prognosis and management for practicing rheumatologists.

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Disease definition and differential diagnosis

As virtually no unique histological or laboratory features have been identified to help in diagnosis, clinical features are instead used to define and diagnose Behçet syndrome (TABLE 1). Although the International Study Group Criteria for Behçet Disease (ISBD) criteria[1] are the most widely used criteria, two important limitations should be noted. Firstly, of the patients with Behçet syndrome who were used to formulate the criteria, close to 80% of patients were from the Middle East (where associated gastrointestinal involvement is infrequent[2]). Furthermore, the control group mainly comprised patients with various connective tissue diseases and not with Crohn's disease or ulcerative colitis; this might have occurred owing to simple oversight or because distinguishing Behçet syndrome from Crohn's disease is difficult. Secondly, the ISBD criteria did not consider symptom prevalence or syndrome prevalence, which is important given the settings in which these criteria were going to be used. To address these issues, a new set of criteria for classification and/or diagnosis of Behçet syndrome has been developed[3], but, like the ISBD criteria, does not take into consideration the baseline probability of any one person having Behçet syndrome in the geographical region where these criteria will be used. This fact is important because Behçet syndrome shows marked geographical differences in prevalence (see below, Epidemiology). Importantly, referring to disease criteria as classification criteria rather than diagnostic criteria does not solve the issue of pre-test probabilities. We argue that separate classification and diagnostic criteria are unrealistic because a diagnosis is nothing more than the application of classification criteria in an individual patient[4].

Behçet syndrome, like all other syndromes, is a construct and we propose this construct has both strong and weak elements (TABLE 2). We define a strong element as a feature that attempts to define Behçet syndrome as a distinct nosological entity — that is, a pathological condition with a unique pathogenesis and more or less unique features that distinguish it from other pathological conditions. By contrast, the weak elements are those features that point to more than one common pathogenetic mechanism[5]. In addition, contrary to the strong elements,

Key points

- Both the disease presentation and evidence from basic studies suggest more than one pathogenetic mechanism is involved in Behçet syndrome. Recognized vascular manifestations in Behçet syndrome include venous claudication, bronchial arterial collaterals (causing haemoptysis) and 'silent' Budd–Chiari syndrome
- The diagnostic specificity of certain manifestations, such as eye disease or vascular involvement, might be more pathognomonic than other manifestations, such as gastrointestinal ulcerations
- In considering the clinical and the basic science findings in Behçet syndrome, the weight of evidence suggests Behçet syndrome should not to be grouped with other, seemingly related, conditions

the value of weak elements in differential diagnosis might differ. Although the presence of subgroups are among the weak elements we list in TABLE 2, they can be useful in diagnosis. For example, the sudden onset of severe headache in a patient with inferior vena caval thrombosis in Behçet syndrome should immediately alert us to the possibility of the presence of a dural sinus thrombosis[6].

Strong elements

Behçet syndrome is rarely present in the absence of a history of recurrent oral ulceration[1]. As such, it is an essential element of the construct because its absence strongly suggests another diagnosis. Three other strong elements have become apparent during the formal data analyses for the ISBD criteria[1] in which the presence of genital ulcers, pathergy (whereby a skin prick a develops into a papule or a pustule) and eye involvement have shown highest numerical discriminatory value to be included in the criteria set. Furthermore, a subsequent factor analysis[7] revealed that eye disease by itself without other variables was disease-defining for Behçet syndrome among 13 other variables examined. Indeed, eye disease as a strong element was also recently supported by a study from Tugal-Tutkun *et al.*[8] in which ophthalmologists examining retinal photographs from patients and suitable diseased controls could identify ocular signs of Behçet syndrome that could be considered diagnostic even in the absence of other clinical information. Recurrent genital ulcerations had the highest discriminatory value in the ISBD criteria. Morphologically, they are similar to oral ulcers, but are deeper, larger and can take longer to heal. Genital scarring is usually strong evidence of the presence of Behçet syndrome. Interestingly, these lesions specifically locate on the scrotum in men and in the labia in women[9], but are more-severe in men[10]. Finally, recent evidence suggests that testosterone increases neutrophil activity in Behçet syndrome[11].

We also consider major vascular disease[12–14] and parenchymal neurological involvement as strong elements. These manifestations are relatively rare compared with skin and mucosal lesions and eye disease, but owing to their unique features have substantial value in differential diagnosis. For example, pulmonary or peripheral arterial aneurysms in a young man (<45 years of age) in an endemic area is very suggestive of Behçet syndrome[15]. In addition, extensive lesions involving the brainstem, basal ganglia or isolated brainstem atrophy are quite unique to and diagnostic of Behçet syndrome[16–18].

Weak elements

Gastrointestinal involvement in Behçet syndrome is one of the four weak elements of the construct (TABLE 2). Distinguishing Behçet syndrome from other inflammatory bowel diseases can be extremely difficult[19] unless other pathologies are present. For example, a study of pathergy in our centre revealed ~10% of patients with inflammatory bowel disease who also had features of Behçet syndrome tested positive to the pathergy skin test, showing how difficult it can be to differentiate Behçet syndrome from inflammatory bowel diseases in general[20]. Additionally, an Immunochip gene-association study among Turkish, Japanese and Iranian patients with Behçet syndrome identified significant risk loci in common with Crohn's disease[21], supporting a common disease mechanism. Accordingly we propose gastrointestinal manifestations are weak elements in the diagnosis.

Another weak element of the construct of Behçet syndrome is the marked geographic variation in its prevalence and severity. Usually, less-severe disease expression is observed in non-endemic areas (see below, Epidemiology section). Although this variation could be the result of differing environmental and/or genetic factors affecting disease expression, the possibility of different disease mechanisms causing similar phenotypes cannot be ruled out given what we understand about Behçet syndrome.

We had previously divided Behçet syndrome into disease clusters or subtypes[5] based on the tendency of certain features to cluster together. Two such clusters are acne–arthritis–enthesitis and vascular disease subsets. The acne–arthritis–enthesitis subset[22] could have been the main reason for the initial inclusion of Behçet syndrome among the seronegative spondyloarthritides[23] by the virtue of some shared clinical features. More recently, interest in this subset has reemerged[24] (see below, MHC-I-opathy section). The vascular disease subset has received increased attention perhaps owing to a wider use of imaging to assess patients. Although vascular manifestations tend to cluster together during the disease course[13], which suggests more than one common pathogenetic mechanism, these can be helpful in diagnosing Behçet syndrome. For example, the onset of haemoptysis in a patient with suspected Behçet syndrome alerts to the presence of a pulmonary artery aneurysm rather than pulmonary emboli, which are not common in Behçet syndrome probably owing to the adherent nature of the venous thrombi seen in this condition[12].

Finally, we consider the different response to various drugs as weak element in our construct. The effectiveness or ineffectiveness of a certain agent to control various manifestations of a disease can give us clues about the underlying disease mechanisms[25]. For example, colchicine is useful for arthritis and erythema nodosum but not particularly effective for skin-mucosa ulcers[26] whereas thalidomide is good for oral ulcers but can exacerbate the erythema nodosum[27]. In addition, etanercept is excellent for treating oral ulcers but has no effect on the pathergy reaction[28]. We consider these varying responses as another indicator of our proposal that more than one disease mechanism is operative in Behçet syndrome.

As is perhaps true in any other disease of unknown aetiology, more information is needed before we are able to develop precise classification or diagnostic criteria. In the meantime, we propose that the weak elements of the construct of Behçet syndrome tell us we should continue to evaluate emerging aetiological clues carefully.

Aetiology and pathogenesis

As for many other inflammatory rheumatological diseases of unknown aetiology, Behçet syndrome had been considered an autoimmune disease for many years. Supportive of this notion were data showing T cell responses to heat shock proteins of *Streptoccus* spp. and *Mycobacterium tuberculosis* as well as autoantibodies against endothelial cells, enolase and retinal S-antigen. However, these events were generally considered to only be related to tissue injury and not directly to the disease pathogenesis[29]. Some clinically important differences between Behçet syndrome and other autoimmune diseases have also been noted, including sex differences in disease expression and a lack of comorbidities with other autoimmune diseases[30]. Interestingly, antibodies to human and mouse neurofibrils that crossreact with *Streptococcus* spp. and *M. tuberculosis* heat shock proteins have recently been shown in Behçet syndrome[31], bringing revived consideration of an adaptive immune response in the pathogenesis — as one would expect in an autoimmune disease.

Behçet syndrome has also been considered an autoinflammatory disease[32]. It is reasonable to consider Behçet syndrome as a polygenic autoinflammatory

Table 1 | **Features helpful in the differential diagnosis of Behçet syndrome**

Feature	Frequently confused with	In Behçet syndrome
Oral ulcers	Recurrent apthous stomatitis	• More-painful, more-frequent and multiple ulcers • Occasional major ulcerations (>1 cm in diameter), sometimes with involvement of the soft palate and oropharynx
Papulopustular lesions	Acne vulgaris	• Present on upper torso and on the extremities • Persistent at older age (>40 years of age)
Genital ulcers	Reactive arthritis and Herpes simplex virus infection or other sexually transmitted infections	• Scar-forming • More-frequent on the scrotum and labia • Rarely occur on the penis shaft, glans penis, cervix or vagina
Erythematous nodular lesions	Erythema nodosum due to a variety of causes	• Multiple, painful and recurrent lesions • Occur in atypical areas (for example, face, buttocks, neck and forearms) • Leave residual pigmentation • Show evidence of vasculitis on histology
Non-granulomatous uveitis	Other causes of infectious and non-infectious uveitis	• Patients are more likely to be male and young (20–30 years of age) • Bilateral and recurrent episodes that mainly involve the posterior pole with isolated anterior segment involvement in ~10% of patients[85] • Characterized by smooth-layered hypopyon, superficial retinal infiltrate with retinal haemorrhages and branch retinal vein occlusion with vitreous haze
Lower extremity vein thrombosis	Idiopathic thrombosis, venous insufficiency and thrombophilia	• Patients are more likely to be male and young (20–30 years of age) • Bilateral involvement with more-frequent relapses with incomplete recanalization and more collateral formation • Both superficial and deep veins are involved • Post-thrombotic syndrome and venous claudication are frequent
Budd–Chiari syndrome	Idiopathic, associated with pregnancy or post-partum and associated with myeloproliferation	• Patients are more likely to be male and young (20–30 years of age) • Frequent occlusion of the inferior vena cava rather than isolated occlusion of the hepatic veins • 'Silent' presentation without ascites • Vascular interventions are unsuccessful
Cerebral venous sinus thrombosis	Idiopathic, Crohn's disease and associated with pregnancy or delivery	• Patients are mostly male and young (20–30 years of age) • Subacute clinical onset is common • Manifests less often with focal deficits and seizures • Venous infarcts are rare
Parenchymal CNS involvement	Multiple sclerosis, sarcoidosis, lymphoma and tuberculosis	• Brainstem and/or basal ganglia are predominantly involved • Lesions are large and confluent, extending from the brainstem to the diencephalon and basal ganglia • Brainstem atrophy is almost pathognomonic
Pulmonary artery involvement (PAI), peripheral arterial or abdominal aortic aneurysms*	Takayasu arteritis or giant cell arteritis	• Patients are more likely to be male and young (<50 years of age) especially when associated with PAI • Uniformly thrombosed • Mostly multiple (PAI) • Usually solitary (for peripheral or abdominal aneurysms) • Associated with fever and increased acute phase response • Occlusions are usually thrombotic • Stenosis or occlusions owing to homogeneous concentric wall thickness are not compatible with Behçet syndrome • Pulmonary arterial aneurysms are almost pathognomonic for Behçet syndrome

Table 2 | **Strong and weak elements* to discriminate Behçet syndrome**

Elements	Explanation
Strong	
Oral ulcers	Absence strongly suggests another diagnosis
Eye disease	• A top discriminatory finding in a formal analysis in formulating disease criteria[1] • A disease-defining factor in a factor analysis [7] • Unique findings found by ophthalmologists masked to disease at other sites [8]
Genital ulceration	A top discriminatory finding in a formal analysis in formulating disease criteria[1]
Major vascular involvement	Pulmonary arterial aneurysms are almost unique to Behçet syndrome[15]
Parenchymal neurological disease	As shown in a comparative and masked study, isolated brainstem atrophy and lesions extending from the brainstem to basal ganglia are quite suggestive of Behçet syndrome[16]
Weak	
Geographical variation in disease expression	• Gastrointestinal disease is more frequent in far-east Asia, especially in Japan, but rather infrequent in Turkey. • By contrast, vascular disease is less common in far-east Asia than in Turkey and other Middle Eastern countries • Milder disease has been reported among patients from non-endemic areas, such as the United States[123]
Association with Crohn's disease	Difficult to distinguish from Crohn's disease if extraintestinal manifestations are not present[19]
Distinct disease subsets	• Vascular disease and acne–arthritis–enthesitis clusters are two important subsets[5] • Presence of these subsets suggests that more than one common pathogenetic mechanism is operative
Different response to various drugs	Varying responses to immunosuppressive treatments could be another indicator of more than one disease mechanism in Behçet syndrome

*A strong element is defined as a feature that attempts to define Behçet syndrome as a distinct nosologic entity with a unique pathogenesis and more or less unique disease features. A weak element points to more than one common pathogenetic mechanism.

disease when Crohn's disease is considered as such. For example, pro-inflammatory IL-1β is increased in active Behçet syndrome, including in the aqueous humour[33]. Additionally, variants of *MEFV* (encoding pyrin, mutations in which play a central part in inflammation in familial Mediterranean fever) as well as mutations in genes encoding the Toll-like receptors, which are important in innate immunity[34], are also present in a minority of patients with Behçet syndrome. However, the proposed clinical similarities between Behçet syndrome and monogenic autoinflammatory diseases such as familial Mediterranean fever are not quite convincing[35]. Indeed, two paramount differences are that almost all autoinflammatory diseases begin in childhood whereas Behçet syndrome frequently begins after puberty and that prominent vasculitis is not a common feature of autoinflammatory conditions whereas at least in a major subset of those with Behçet syndrome patients display vascular involvement. Furthermore, IL-1β blockade, which has been quite successful in treating autoinflammatory diseases, has not been convincingly successful in Behçet syndrome[36].

Here, we propose that because a common and dominant pathological factor for Behçet syndrome has not been identified, and that it is possible that there is no single common denominator, referring to Behçet's as a syndrome rather than a disease is preferable. That is, the current evidence for disease definition and disease mechanisms in Behçet's suggests 'splitting', in which searching for what is unique about Behçet's, will be more fruitful than 'lumping' in which likeness with other conditions is sought. We will briefly elaborate on 'lumping' in discussing attempts to consider Behçet syndrome as a MHC-I-opathy.

MHC-I-opathy?

The concept of seronegative spondyloarthritides (SpA) was introduced in 1974 to describe rheumatoid factor negative inflammatory arthritis, which predominantly involves the axial skeleton and sacroiliac disease. Patients with this group of diseases are also frequent carriers of *HLA-B*27*. Initially, Behçet syndrome had been included in this group[23]; however, it was soon realized that patients with Behçet syndrome were carriers of *HLA-B*51* rather than *HLA-B*27* and that axial skeletal arthritis was not prominent in these patients, leading to the removal of Behçet's from the SpA concept[37]. Recently, the debate on whether this classification was correct has been rekindled, owing to two observations[24]. Firstly, important data have emerged that some of the inflammatory pathways considered operative in the seronegative SpA ankylosing spondylitis (AS) and psoriatic arthritis (PsA), such as the IL-10 and IL-23–IL-17 pathways, have also been observed in Behçet syndrome[24,38]. Secondly, as mentioned, acne and arthritis commonly occur in patients with Behçet syndrome and these patients also commonly have enthesitis[22], which is a phenotypic feature related to the SpA.

Evidence in support of Behçet syndrome being related to AS and PsA also stems from the most important genetic risk factor for Behçet syndrome, *HLA-B*51* (REF. 24), which is an MHC class I allele. The gene was found to be epistatic with *ERAP1*, which encodes endoplasmic reticulum aminopeptidase 1 — a molecule in the endoplasmic reticulum that prepares (trims) peptides for presentation to effector cells by MHC class I molecules[38–40]. Importantly, polymorphisms in *ERAP1* have also been reported as important as susceptibility loci for PsA and AS[41,42]. Mechanistically, altered trimming of either exogenous (such as microbial) or endogenous peptides by the *ERAP1* variants might render them disease-promoting or disease-preventing.

Given that Behçet syndrome, AS and PsA are associated with variants in *HLA* genes encoding MHC class I, it is interesting to note that variants in these genes are also either disease-promoting (in AS) or disease-preventing (in Behçet syndrome[24]). This observation has led to the concept of 'MHC-I-opathy' (REF. 24), and is supported by the following observations. Firstly, the different HLA allele associations determine disease tissue-localized manifestations; for example, *HLA-B*51* is associated with eye or skin disease in Behçet syndrome, *HLA-C*0602* is associated with skin lesions and increased disease severity in PsA and *HLA-B*27* is associated with enthesitis and eye involvement in AS. Secondly, localized areas of stress, such as the entheses in AS and Behçet syndrome, or the skin, such as in the pathergy phenomenon in Behçet syndrome and the Koebner phenomenon in psoriasis are important in triggering innate immunity. Thirdly, the immune and inflammatory responses in these diseases all share elements of both innate and adaptive pathways.

In the MHC-I-opathy concept, more weight is given to the innate immune response than to the adaptive immune response, suggesting that the adaptive response facilitates the induction of inflammation rather the inflammation driving the disease[24]. This emphasis is similar to that which has been placed on the innate immune response as central in the pathogenesis of AS and PsA[43]. The adaptive immune response aspect of the MHC-I-opathy concept is mediated by cytotoxic T cells, in which putative antigens presented by the MHC class I molecules activate T helper 1 (T_H1) and T_H17 cell pro-inflammatory activity[24]. However, other cell interactions might be culpable in the pathogenesis of Behçet syndrome. For example, although altered antigen presentation by the MHC encoded by *HLA-B*51* in patients not carrying protective *ERAP1* polymorphisms is indeed important in causing tissue injury, the mechanism might not rely on cytotoxic T cells[44]. Instead, antigen presentation might occur mainly to natural killer cells[44]. Additionally, the presence of *HLA-B*51* does not readily explain the cytokine polarization profile observed in the condition[44].

Not restricted to a discussion of the MHC-I-opathy concept, which does not seemingly assign a specific role to *HLA-B*51* in cytokine polarization[44], a consideration of the mechanisms of cytokine control is also needed. In Behçet syndrome, the Janus kinase (JAK) and signal transducer and activator of transcription (STAT) pathway is important[45]; Tulunay and colleagues investigated this canonical pathway in peripheral blood mononuclear cells from those with Behçet syndrome using whole-genome microarray profiling[46]. They observed increased JAK–STAT signalling in both CD 4^+ T cells and $CD4^+$ monocytes compared with the healthy controls. The authors speculated this signalling stems from activity of T_H1 and T_H17-type cytokines, such as IL-2, IFNγ, IL-6, IL-17 and IL-23, and not through T_H2 cell activation as one would expect in an MHC class II-associated autoimmune disease.

A microbial trigger?

As in other inflammatory conditions of unknown aetiology, interest in finding a microbial cause for Behçet syndrome has been pursued[47]. However, thus far no single pathogen has emerged as a likely candidate. Oral infections, which had originally been proposed by Behçet himself to be a trigger[48], have continued to be proposed as disease-inciting[49]. A collaborative study, the first formal microbiome study in Behçet syndrome[50], proposed a distinct salivary signature. This study revealed less bacterial diversity in individuals with Behçet syndrome than among healthy controls; in a subset of patients, periodontal treatment corrected the oral health issues but not the bacterial distribution. Whether these findings in the oral flora are causative of Behçet syndrome or a consequence of the condition is unclear[51].

The intestinal microbiota are also beginning to be studied in Behçet syndrome and a proposal for a specific microbiome signature — namely, a paucity of genera *Roseburia* and *Subdoligranulum* along with a decrease in butyrate production — has been made and, more recently, an abundance of bifidobacteria has been described[52,53]. In line with these findings, mutations in *FUT2*, which encodes the fucosyltransferase 2 present in intestinal and oral epithelial cells, has been reported in Behçet syndrome[54] — similar to what has been reported in patients with Crohn's disease[55]. Epithelial α1,2-fucose molecules formed by the enzymatic action of fucosyltransferase 2 are important to bacterial symbiosis in the gut and also form a barrier against pathogenic bacteria[56]; mutations in *FUT2* impair this barrier.

Epigenetics

Epigenetic information is becoming increasingly available in Behçet syndrome. For example, differential methylation of genes associated with cytoskeletal remodelling and cell adhesion in circulating $CD4^+$ T cells and monocytes have been identified in patients with Behçet syndrome[57]. Importantly, these changes revert to normal after treatment, particularly for genes involved in microtubule structure (*KIFA2* and *TPPP*)[58], suggesting that, with further validation, methylation patterns might be useful as biomarkers or theurapeutic targets.

Micro RNAs, another main form of epigenetic influence have also been studied. T_H17 cell effects have attracted particular attention in the light of miR-155 expression; however, the work is still in its nascent state

and the results are somewhat conflicting[58]. In brief, epigenetic influences are particularly important and deserve more attention in Behçet syndrome in that they might be instrumental in explaining the geographical and envorinmental differences that are prominent in this condition[59].

Summary

As we try to outline above, there is more to know about the disease mechanisms in Behçet syndrome. Importantly, we currently have much better insight about how *HLA-B*51*, the most established risk factor for Behçet syndrome, might be operative in pathogenesis. On the other hand, the frequency of *HLA-B*51* is ~60% even in areas where Behçet syndrome is endemic[60] and is much lower in other regions. This frequency certainly implies the *HLA B*51* association cannot wholly explain what we call Behçet's today. Furthermore, none of the data discussed adequately address important manifestations of Behçet syndrome, such as thrombosis (with its resistant thrombi[61]) or the unique parenchymal brain disease. Taken together, we consider the current evidence supporting the notion that Behçet's is a syndrome rather than a disease.

Epidemiology

Further underlying the complexity of classification and definition of Behçet syndrome are regional differences in disease expression. Behçet syndrome is sometimes referred to as the Silk Route disease because of its frequency in the Middle East and far-east Asia (FIG. 1); these regions have traditionally been considered the endemic areas for the condition[62]. However, increasing awareness of the condition along with the recent increases in human migration is changing this view. For example, Behçet syndrome was traditionally viewed as very rare among black individuals, but a study from Dakar, Senegal, reported a case series of 50 patients with Behçet syndrome with a proposed yearly incidence of 3.84 per 100,000 population[63]. Another study showed that 70% of patients in southern Sweden were of non-Swedish ancestry[64]; studying immigrant populations in traditionally non-endemic areas can provide useful insights into gene–environment interactions and enable us to identify environmental and perhaps modifiable risk factors.

For example, both Germany and the Netherlands have sizeable Middle-Eastern immigrant populations[65,66]. In both countries, the prevalence of Behçet syndrome among immigrants is lower than that reported in their countries of origin, but higher than that among

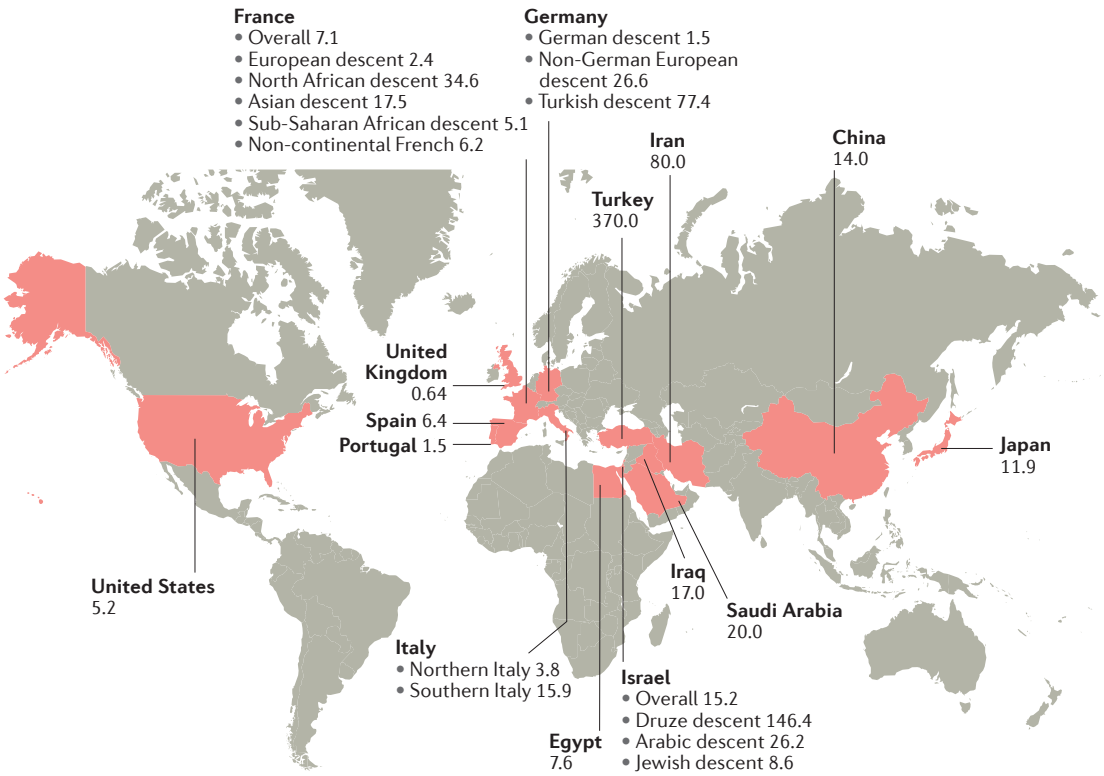

Figure 1 | **The prevalence of Behçet syndrome.** Prevalence (shown as people per 100,000 population) of Behçet syndrome is higher along the ancient Silk Route (for example, Turkey, Iran, Japan and Korea) than in other parts of the world[1,23]. Prevalence also increases from north to south, with much lower figures in the United Kingdom than in Italy and Spain. Immigration patterns also seem to have an increasing influence on Behçet syndrome prevalence in Europe and have provided interesting insights. For example, studies from Germany and the Netherlands have shown that although prevalence is higher in immigrant populations than the general German or Dutch populations, this prevalence is somewhat lower than that in the countries of origin[65,66].

native Germans and Dutch[65,66]. The Dutch study from Rotterdam reported that a minority of patients from immigrant backgrounds (14 out of 72 patients, 19%) were indeed born in the Netherlands[66]. Accordingly, it would be of interest to know the prevalence among those who had recently migrated to the Netherlands compared with second-generation or third-generation immigrants to better understand the role of environment factors in pathogenesis.

In contrast with the German and Dutch studies, data from immigrants living in Paris, France, have indicated that the frequency of Behçet syndrome is not different than that in the countries of origin[67], which would provide another avenue for understanding the influence of environmental factors on prevalence. However, the study was a survey-based report in socially underprivileged areas of Paris, which raises the possibility of socioeconomic factors influencing the results.

In the United States, an estimated prevalence of 5.2 per 100,000 population was reported between 1996 and 2005 (REF. 68). Contemporary US data has been collected in New York, New York, since 2005 (REF. 69). Among 313 consecutive patients, those with a northern European background had more gastrointestinal disease (81 out of 172 patients, 47%) compared with the group of patients who were ethnically from endemic areas (40 out of 141 patients, 28%); this difference was statistically significant ($P = 0.001$)[69]. For the whole New York cohort, less eye disease and vascular involvement than other centres from Turkey and Japan was reported[69]. Approximately one-third of patients had eye disease in each group; interestingly with only one blind eye in total. Similarly, milder disease has also been reported among patients from other non-endemic areas[70].

Clearly, more comparative epidemiology work is needed in Behçet syndrome to guide us in diagnosis, for fair allocation of resources and perhaps decipher the disease mechanisms in this very complex condition. Perhaps in comparative formal hospital-based surveys, which use the frequencies of other diseases, such as rheumatoid arthritis, that do not have apparent differences in frequency across different geographies, Behçet's can be of help[71].

Clinical manifestations

Clinical manifestations in Behçet syndrome are variable and characterized by unpredictable periods of recurrences and remissions, although the frequency and severity tend to abate with time. Skin-mucosa lesions are the most common manifestation and are usually the presenting symptoms, whereas ocular, vascular and neurological involvement are less common but more serious[10,12,14,17,18]. The overall mortality rate of patients with Behçet syndrome is significantly increased among younger men (<25 years of age) and early in the disease course among those with major organ involvement. In a 20 year follow-up study of a large inception cohort in our dedicated clinic ($n = 428$, of which 286 were male and 142 were female), a total of 42 (39 male, 3 female) patients had died at the end of the survey[10]. Age-matched standardized mortality ratios were specifically increased among young males (that is, the 14–24 years of age and 25–34 years of age groups) whereas older males (35–50 years of age) and females had a normal lifespan. Furthermore, the mortality rate was highest early after disease onset (the first 7 years) and had a tendency to decrease with time. Major causes of mortality were large vessel disease and parenchymal central nervous system (CNS) disease. Later, a French group showed a mortality rate of 5% during a median follow-up of 8 years in a cohort of 817 patients[72]. Factors associated with mortality in this study were similar to what we observed[10].

Quality of life is impaired in Behçet syndrome, with fatigue being an important problem that is correlated with quality of life, disease activity, depression, anxiety and physical functioning[73–76]. Suicidal ideation is more frequent among patients with major organ involvement; pain, impaired quality of life, depression, CNS involvement and past prednisolone use have been shown to be independent predictors of suicidal ideation[77].

Oral ulceration

Oral ulcerations are usually the first as well as the most frequent symptoms. Minor aphthous ulcers (<10 mm in diameter) are the most common type. Although quite similar to recurrent aphthous stomatitis, oral ulcers in Behçet syndrome could be multiple, more painful and more frequent. Local trauma, certain types of food, menstruation and cessation of smoking are described as triggering factors[78]. The frequent occurrence of attacks of oral ulceration during early Behçet's was found to predict the development of major organ involvement among male patients[79]. Oral ulcers continue to develop for many years after disease onset[80], but all other manifestations usually resolve[10].

Eye involvement

Lesions — such as a smooth-layered hypopyon (a leukocytic exudate in the anterior chamber of the eye), superficial retinal infiltrates with retinal haemorrhages and branch retinal vein occlusion with vitreous haze — were identified as pathognomonic for Behçet syndrome uveitis as indicated above[8]. Specialized imaging techniques such as optical coherence tomography (OCT) and fluorescein angiography are becoming useful tools in the diagnosis and assessment of disease activity[81–83]. Additionally, central foveal thickness has been suggested as a non-invasive measure to assess inflammatory activity in early uveitis[82] and localized non-glaucomatous retinal nerve fibre layer defects, as an indicator of posterior pole involvement[83].

The prognosis of eye disease has improved in recent years. For example, Chung *et al.*[84] reported that mean visual acuity was better among patients whose first visit to a dedicated Behçet syndrome clinic in Korea was between 2004 and 2010, than those who registered between 1994 and 2000. Similarly, Cingu *et al.*[85] reported that the risk of losing useful vision was lower in patients in Turkey who presented between 2000 and 2004 than in patients who presented between 1990 and 1994. They observed that the risk of having loss of useful vision at

3 years of follow-up decreased from 27.6% (43 out of 156 eyes) in the 1990s to 12.9% (26 out of 201 eyes) in the 2000s. In line with this finding, risk of having loss of useful vision was 13% at 10 years of follow-up in a study by Taylor *et al.*[86] in the United States and 14.4% at 1-year of follow-up in a study by Accorinti *et al.*[87] in Italy.

Vascular involvement

Except for non-pulmonary arterial disease, which occurs at a later age (≥40 years of age), 75% of patients with Behçet syndrome experience their first vascular event within 5 years of disease onset[13]. Additionally, the cumulative relapse rate of vascular events was found to be 23% at 2 years and 38% at 5 years[13]. In the vascular subset (see above and TABLE 2), several types of vascular manifestation tend to occur in the same individual, creating statistically significant associations across all patients; for example, cerebral venous sinus thrombosis and pulmonary artery involvement (PAI) tend to co-occur, as do intracardiac thrombosis and PAI, and Budd–Chiari syndrome and inferior vena cava syndrome[12–14].

Lower extremity vein thrombosis (superficial and deep) is the most common form of vascular involvement and leads to severe post-thrombotic syndrome and venous claudication[88] (FIG. 2a). PAI can manifest as pulmonary arterial aneurysms and single *in situ* pulmonary arterial thromboses[12] (FIG. 2b). A wide range of pulmonary parenchymal lesions such as nodules, consolidations and cavities are also part of the vascular manifestations[12]. Mild elevation of pulmonary arterial pressure can be associated with PAI[89] and bronchial arterial collaterals emerge as another cause of haemoptysis in patients with Behçet syndrome who are in remission[90]. Aneurysms or thromboses can regress in ~70% of patients with immunosuppressive treatment[12]. The relapse rate is ~20% and mortality rate is ~25% at 7 years, despite tight control of disease activity, frequent medical visits and aggressive management[12]. Increased diameter of the aneurysms and high pulmonary arterial pressures at presentation are poor prognostic factors for survival[12].

Budd–Chiari syndrome mostly involves the inferior vena cava (the suprahepatic and hepatic segments) and the hepatic veins. In patients who present with ascites (FIG. 2c), the mortality rate is ~60% within a median of 10 months after diagnosis[14]. However, in some patients, Budd–Chiari syndrome develops gradually without ascites. Imaging studies using ultrasonography or CT show that these individuals have efficient collateral formations. These 'silent' patients have more favourable outcomes, with <10% expected mortality at 7 years[14].

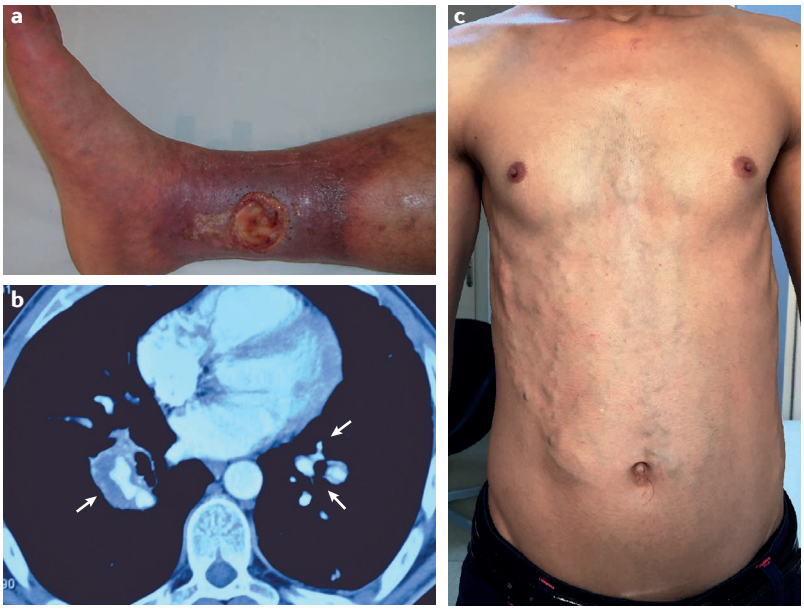

Figure 2 | **Vascular involvement in Behçet syndrome.** Vascular involvement is an early and relapsing event in Behçet syndrome and occurs in up to 40% of patients. **a** | Ulceration on the distal tibia in a 34-year-old male patient. Superficial and deep femoral vein thromboses were the initial symptoms, which recurred despite immunosuppressive treatment. Eventually, post-thrombotic syndrome with ulceration, oedema, induration, hyperpigmentation and superficial skin collaterals developed. **b** | Bilateral, multiple pulmonary arterial aneurysms (arrows) on a CT scan of a 28-year-old male with Behçet syndrome who presented with haemoptysis, chest pain, dyspnoea and fever. Additionally, mural thrombosis inside the aneurysms can be observed. **c** | Thorax of a 26-year-old male with juvenile-onset Behçet syndrome who presented with ascites, abdominal pain and fever. The hepatic segment of the inferior vena cava and all three hepatic veins were occluded with thrombi. Intensive immunosuppressive treatment resolved most of the symptoms, although he subsequently developed bilateral gynaecomastia and diffuse abdominal collaterals, which can be ascribed to residual mild liver insufficiency.

CNS involvement

CNS disease occurs in 5–10% of patients with Behçet syndrome, mostly in the form of parenchymal brain involvement. Brainstem involvement is the most characteristic type of involvement. Pyramidal signs, hemiparesis, behavioural–cognitive changes, sphincter disturbances and/or impotence are the main clinical manifestations of CNS involvement. Psychiatric problems might also develop in some patients[91].

Sometimes, the clinical presentation of CNS disease in Behçet syndrome can be taken for multiple sclerosis, in which case MRI findings are helpful[91]. In contrast to the large extensive lesions of CNS involvement in Behçet syndrome, multiple sclerosis has more discrete and smaller brainstem lesions. Optic neuritis, sensory symptoms and spinal cord involvement, which are common in multiple sclerosis, are seldom observed in Behçet syndrome. White matter lesions are also different: in multiple sclerosis, lesions tend to be supratentorial and periventricular with corpus callosum involvement, whereas in Behçet syndrome, lesions are small, bihemispheric and subcortical. The cerebrospinal fluid patterns also differ: pleocytosis is more prominent in multiple sclerosis, whereas oligoclonal band positivity (that is, the gold-standard test for multiple sclerosis) is rarely observed in Behçet syndrome[91].

Compared with patients with multiple sclerosis, patients with Behçet syndrome who have CNS involvement have poorer performance on several measures of cognitive status[92]. Moreover, a subgroup of patients with Behçet syndrome may present with multiple sclerosis-like features on MRI[93]. These patients were more likely to be female, to have increased number of neurological attacks, to have a higher rate of oligoclonal band and to

have less pleocytosis. This implicates that disease mechanisms in multiple sclerosis and Behçet syndrome might be similar. Finally, quantitative analysis of the brainstem by MRI has been suggested as an effective diagnostic tool for, as well as in monitoring the evaluation of disease activity in, chronic progressive Behçet syndrome with CNS involvement[94] (FIG. 3).

Finally, Noel *et al.*[95] investigated the outcomes of a large cohort of patients ($n = 115$) with CNS involvement, excluding dural sinus thrombosis. The authors found that after a median follow-up of 6 years, 30% of patients relapsed after immunosuppressive treatment, 25% of patients became dependent on care takers and 10% had died[95].

Gastrointestinal involvement

Gastrointestinal involvement in Behçet syndrome resembles Crohn's disease in its presentation, with abdominal pain and diarrhoea that may be accompanied by bleeding, and is an uncommon manifestation in geographies other than in far-east Asia[2]. Behçet syndrome usually causes round or oval ulcers most commonly in the terminal ileum[96]. Ulcers are usually deep, large and single with a tendency to perforate or cause massive bleeding. Mucosal biopsies show chronic or active mucosal inflammation as well as vasculitic findings in a small proportion of patients[96]. Faecal calprotectin levels are associated with disease activity, similar to Crohn's disease[97]. Even with treatment, relapses may occur in ~20% of patients[96].

Management and outcome measures

The goals of management in Behçet syndrome are to rapidly suppress inflammatory exacerbations and to prevent relapses to maintain good quality of life and preserve organ function. A treat-to-target strategy has not been well established owing to a lack of standardized outcome measures that define remission, low disease activity or a target score (or level of change from baseline) that predict a better outcome. Although several outcomes and outcome measures have been used in clinical trials, many of these have not been validated or widely accepted[98]. The variability in outcomes and outcome measures has made it difficult to compare the efficacy of treatment modalities and help make treatment decisions[99]. Furthermore, the assessment of Behçet syndrome is complicated owing to the frequently relapsing but less-disabling skin, mucosal and joint involvement against a backdrop of the less-frequent but more-serious (and even life threatening) nature of major organ involvement. Efforts are ongoing to develop a core set of outcome measures for Behçet syndrome clinical trials[100].

Despite these difficulties, management can still be individualized depending on what we know regarding the prognoses of patients with Behçet syndrome. This approach is also emphasized in the 2016 EULAR recommendations[101]. Younger patients and male patients who have higher risk of severe disease should be followed-up closely for the development of major organ involvement and treated aggressively when such involvement is noted.

Skin, mucosal and joint involvement

The management of patients with only skin, mucosal and joint involvement is determined by the frequency and severity of their lesions and the extent to which these lesions impair their quality of life. The patient's perception and preferences are important in making treatment decisions as these lesions do not cause damage and are neither organ-threatening nor life-threatening.

Topical treatments such as corticosteroids help to decrease the severity and duration of lesions and can be used without the need of continuous systemic treatment in patients whose recurrences are infrequent and do not cause much discomfort. Systemic treatment modalities are used when it is necessary to prevent recurrences. Colchicine is usually the initial choice of treatment owing to its safety profile and low cost (FIG. 4). However, it has limited efficacy, especially for oral ulcers.

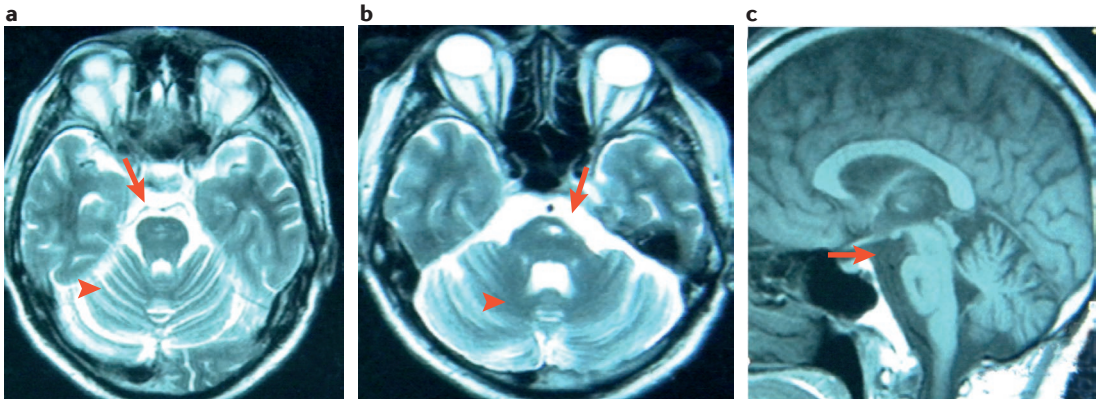

Figure 3 | **CNS involvement in Behçet syndrome.** Cranial MRI scans a 30-year-old male patient with Behçet syndrome of 12 years' duration. Central nervous system (CNS) involvement began 10 years after diagnosis with severe headache, speech difficulties, swallowing problems and cognitive disturbances. **a** | MRI T2-weighted axial sequence show pontine (arrow) and cerebellar (arrowhead) atrophy. **b** | Also evident are an ischaemic lesion on the pons (arrow) and fourth ventricle dilatation (arrowhead), which are other characteristic lesions of brainstem atrophy. **c** | Sagittal sequence similarly shows the same lesions (arrow).

Lactobacilli lozenges might be used[102]. Apremilast (a phosphodiesterase 4 inhibitor) was shown to be relatively safe and effective for oral and genital ulcers[103]. Thalidomide, IFNα and etanercept are other alternatives for refractory skin, mucosal and joint lesions[27,28,104].

In terms of emerging treatments, a small open-label study of anakinra (an IL-1 receptor antagonist) for skin-mucosa involvement showed that only two out of six patients had no oral ulcers on two consecutive monthly visits[105]. The dose had to be increased (to 200 mg per day from 100 mg per day) in all but one patient after 1 month. Additionally, an open-label prospective study of ustekinumab (which inhibits IL-12 and IL-23) showed a decrease in the median number of oral ulcers from two ulcers to one ulcer after 12 weeks[106].

Major organ involvement

Patients with major organ involvement should be treated effectively to prevent damage. Posterior uveitis is managed with immunosuppressive agents such as azathioprine, ciclosporin, IFNα and anti-TNF antibodies (such as infliximab) together with glucocorticoids. The decision to use IFNα or anti-TNF agents as first-line treatment or to save these for patients with uveitis who fail or relapse on azathioprine and/or ciclosporin depends on the severity of the eye involvement, experience of the physician and reimbursement policies. Furthermore, head-to-head controlled trials are needed to demonstrate the superiority of IFNα or anti-TNF agents in Behçet syndrome and to identify any patient characteristics that would mandate the use of one of these agents or the other.

Anti-IL-1, anti-IL-6 and anti-IL-17 agents have also been tried in patients with refractory eye disease. A pilot study and an uncontrolled phase II study, both with small numbers of patients, showed beneficial results with the IL-1 blocker gevokizumab[107,108]; the randomized controlled trial of this agent was terminated as it did not achieve its primary end point[36]. Secukinumab (which inhibits IL-17A) had also failed to meet its primary end point of reduction of uveitis recurrence in a randomized controlled trial[109]. A systematic review of case reports and a small case series with tocilizumab (an IL-6 receptor inhibitor) in patients refractory to IFNα and infliximab suggest that this agent may be effective in protecting visual acuity, reducing central macular thickness and improving fluorescein angiography findings[110,111].

Arterial aneurysms are treated with high-dose glucocorticoids and monthly cyclophosphamide pulses followed by maintenance therapy with azathioprine[112] (FIG. 4). Surgery might be required for peripheral artery aneurysms[113]. Anti-TNF agents can be used in patients who fail to respond to this regimen[114]. Consensus among experts is that immunosuppressive treatments such as azathioprine or ciclosporin should be used for deep vein thromboses as in Behçet syndrome these result from inflammation of the venous wall rather than a pro-coagulant state[115]. The use of anticoagulants is

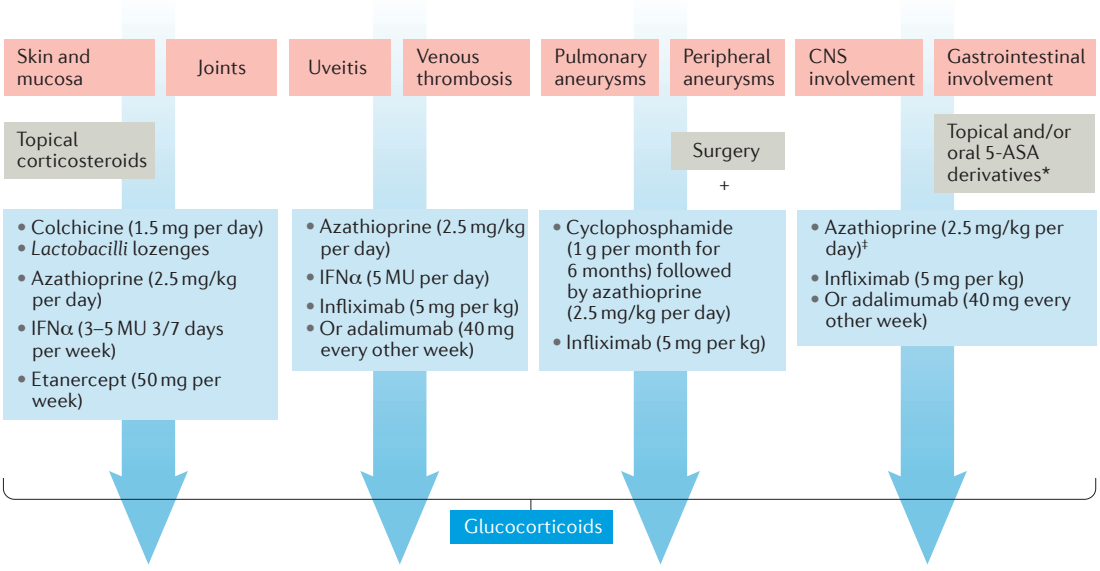

Figure 4 | **Management of Behçet syndrome.** Treatment is individualized to each patient according to the type and severity of organ involvement, patient age, patient sex and disease duration. In our centre (Cerrahpaşa Medical Faculty, Turkey) patients with only skin-mucosa involvement and joint involvement can be managed with topical agents and colchicine. Those who continue to have bothersome lesions despite these measures can be prescribed immunosuppressive or immunomodulatory agents such as azathioprine, IFNα, thalidomide, apremilast or anti-TNF agents. In patients with eye, vascular, central nervous system (CNS) or gastrointestinal involvement immunosuppressive agents such as azathioprine are used as first-line treatments. Biological agents such as IFNα or anti-TNF antibodies are used in patients refractory to immunosuppression. Cyclophosphamide is usually the first choice for the initial treatment of arterial aneurysms that are life threatening. Pulmonary lobectomies in cases of giant pulmonary arterial aneurysms, or surgical resection of peripheral large aneurysms, can also be performed after immunosuppressive treatment. Glucocorticoids can be used for rapid suppression of inflammatory flares to prevent damage in all types of involvement. 5-ASA, 5-aminosalicylic acid. *Mild cases. ‡Moderate and severe cases.

controversial because case–control studies have not shown a beneficial effect in preventing relapses of deep vein thromboses[116], but controlled data are needed to verify this finding and to understand whether other benefits, such as preventing post-thrombotic syndrome, exist.

Parenchymal CNS involvement is treated with high-dose glucocorticoids together with immunosuppressive therapy such as azathioprine or anti-TNF agents; ciclosporin is avoided as it is neurotoxic[117]. The role of IL-6 blockers, which seem promising for CNS involvement based on a small case series[110] (in which high IL-6 levels were observed in the cerebrospinal fluid of patients with CNS disease[118,119]) need to be further explored.

The initial management of gastrointestinal involvement is with 5-aminosalicylic acid derivatives in patients with mild disease. In those with moderate or severe gastrointestinal involvement, azathioprine is recommended[96]. Anti-TNF agents and thalidomide can be used in patients with refractory gastrointestinal involvement[120] (FIG. 4).

Finally, a systematic review of patients with Behçet syndrome treated with haematopoietic stem cell transplantation for either refractory major organ involvement or a comorbid haematological condition showed that this approach was successful in inducing remission of Behçet syndrome lesions in 18 of 19 patients[121]. However graft-versus-host disease and infections occurred in some of the patients and one patient died owing to infection after 2 months.

Conclusions

The management of Behçet syndrome is increasingly successful, even if the precise definition of the condition is lacking. Indeed, Behçet syndrome is a complex construct with what we propose as strong and weak elements. The strong elements are those clinical findings the presence or absence of which differentiate Behçet's from other diseases or syndromes. The weak elements, on the other hand, are features that suggest more than one pathogenetic mechanism might be involved in Behçet's and might also be useful in differential diagnosis.

The clinical picture of Behçet syndrome is further complicated by a lack of specific histopathology or laboratory components that can be used in diagnosis. As said, the precise disease mechanisms that underlie the symptoms are not fully deciphered and difficult to do so owing, in part, to regional differences in disease expression. Despite advances in molecular genetics and in understanding potentially implicated inflammatory pathways (for example, those related to *HLA-B*51*) the current construct of what comprises Behçet syndrome remains rather complex. More basic, translational and clinical work is needed, with emphasis placed on understanding phenotypic expression and geographic influence. Additionally, as evidence continues to emerge on Behçet syndrome, a clearer definition should emerge — we believe, encouraging a splitters approach and allowing Behçet syndrome not to be grouped with other, somewhat related, conditions[122].

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