

# Behçet's syndrome: a critical digest of the 2013-2014 literature

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### ABSTRACT

*This review focuses on the recent research on the epidemiology, outcome measures, immunopathogenesis, genetics, clinical manifestations and management of Behçet's syndrome (BS). A systematic review of outcomes and outcome measures used in BS points out to a need for reliable and validated outcome measures that would be widely used by researchers. Despite novel methods of analyses and cheaper and more sophisticated technologies are yielding new genetic associations and molecular pathways in BS, HLA-B51 still shows the strongest link. The MHC class I amino acid residues, GIMAP, the neuromodulin pathway, complement component copy variations, microRNA polymorphisms and DNA methylation abnormalities are examples. IL-27, 33 and 37 may also play important roles in the pathogenesis. Clinical studies have shown that the fluorescein angiography scoring system could be a useful tool to discern active inflammation in eye disease from the quiescent phase, the cumulative risk for recurrence of any vascular event was 38% at 5 years in a large vascular cohort and significant correlations between dural sinus thrombosis and pulmonary artery involvement, a retrospective survey of patients with parenchymal NBS revealed a 30% relapse rate and 10% mortality of 10% after a median follow-up of 73 months, and quantitative measurement of the brainstem atrophy using MRI was correlated with clinical symptoms. Studies on the management of BS showed that continuous use of colchicine may not prevent the development of organ involvement at the long-term, remission of uveitis may persist after withdrawal of infliximab, refractory intestinal involvement may respond to infliximab, immunosuppressive treatment is important in reducing complications of endovascular stent*

*grafting for aortic pseudoaneurysm and intravitreal steroid implants or injections may be considered in refractory uveitis.*

### Introduction

Behçet's syndrome (BS) is a multisystem vasculitis with unknown etiology. There are several new and exciting publications that help our understanding of BS, and that may help to guide physicians in patient care. In this year's critical digest we reviewed articles published during 2013 and 2014 and selected articles focusing on epidemiology, outcome measures research, immunopathogenesis, genetics, clinical manifestations and management.

### Epidemiology

A recent survey from France compared the clinical features and prognosis of BS patients with different ethnic backgrounds followed in the same unit (1). The cohort was composed of 369 European, 350 North African, and 50 sub Saharan African patients. They observed that the sub Saharan African BS patients were more commonly male, had more CNS involvement, lower frequency of HLA B51 and higher mortality rate. Although not statistically significant, the frequency of cardiovascular involvement was also higher in this group (41% among Europeans, 43% among North Africans and 54% among sub Saharan Africans). Whether this worse prognosis in sub Saharan African patients reflects a difference in referral patterns or access to health sources, leading to more severe patients being followed in this university hospital, needs to be further delineated. Although the authors indicate that the French social security system covers all medical care, the fact that immunosuppressive use rate is not higher in sub Saharan African patients (48% among Europeans, 59% among North Africans

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and 52% among sub Saharan Africans) despite more CNS and cardiovascular involvement may also support the contention that socioeconomic factors may play role in the higher mortality rate in this group.

Another study, this time focusing on geographic differences, compared clinical manifestations and activity of BS in the United States (US) and in Turkey (2). Consecutive patients from 2 centers in the US (National Institute of Health and New York University) and a center in Turkey (Istanbul University Cerrahpasa Medical School) were included. The survey showed that American patients were more likely to be female and have longer disease duration, and more likely to have gastrointestinal and neurologic disease. Eye and vascular disease, however, were similar in frequency in both USA and Turkish patients. Behçet's Disease Current Activity Form (BDCAF) and Behçet's Syndrome Activity Scale (BSAS) were used to assess activity and Behçet's Disease Quality of Life measure (BDQoL) was used to assess quality of life. BDCAF is a patient and physician composite measure and BSAS and BDQoL are patient reported outcome measures. The survey showed that disease activity and quality of life scores were worse among the American patients. However, this may reflect differences in referral patterns between the two centres, more severe patients being diagnosed and referred to the American centres, or differences in patient perception resulting from cultural differences, rather than an actual difference in disease severity. A formal evaluation of severity of each type of involvement was not performed in this study.

A change in the disease expression of BS has been reported from different countries over the past years, and a change in environmental factors, possibly hygiene, or differences in management strategies was proposed as an explanation (3). Korean colleagues retrospectively evaluated their 3674 BS patients, divided into decades, to see whether the clinical expression of BS has changed over the last 3 decades (4). They found that, male sex, complete type of BS and major presenting features such as genital ulcers, ocular in-

volvement and skin lesions significantly declined, whereas the mean patient age increased progressively, as did the frequencies of joint, gastrointestinal and CNS manifestations. In addition to the previous explanations such as the role of hygiene and medications, the authors proposed that increased awareness and greater accessibility to the hospital may be responsible for these changes.

Two other groups from different parts of the world reported the demographic and clinical features and treatment modalities of their BS patients. In the Spanish series including 496 patients from 16 centres, with a median follow-up of 134.9 months, eye involvement was present in 45.1%, joint involvement in 34.7%, venous thrombosis in 19.7% and CNS involvement in 13.5% and gastrointestinal involvement in 1.4% (5). Among these patients, colchicine was used by 73.8%, glucocorticoids were used by 77.6%, at least one immunosuppressive was used by 52.2% including biologics by 12.5%. The other series was from Russia, including 250 patients with various ethnic backgrounds including Chechnya (21.6%), Dagestan (19.2), Azerbaijan (14.4%) and Armenia (8.8%) (6). The frequency of eye involvement was 54%, joint involvement 53%, vascular involvement 25%, neurologic involvement 8% and gastrointestinal involvement 25%. Gastrointestinal involvement was confirmed by endoscopy in all of the patients, and the high frequency of gastrointestinal involvement in this group of patients originating mostly from Central Asia, resembles that in the Far East.

#### *Outcome measures in Behçet's syndrome*

Reliable and valid outcome measures are needed to measure the response to treatment modalities and to be able to compare different patient populations and interventions in order to develop management strategies. A systematic literature review was conducted on outcome measures used in randomised controlled trials, observational intervention trials, longitudinal cohorts and biomarker studies in BS (7). This review revealed that a total of 139

outcomes or outcome measures were used in a total of 248 studies. Some of these were tools that were specifically developed for BS such as BDCAF and BDQoL. Others were organ-specific outcomes or outcome measures. Some measures were developed for other diseases. Among these were the Crohn's disease activity index or multiple sclerosis functional compound scale. And finally, there were generic outcome measures used for various rheumatologic and non-rheumatologic conditions such as SF-36. This systematic review showed that despite the presence of numerous outcomes and outcome measures which were used in BS trials, few were validated and widely used. Moreover, there was a lack of validated and widely used outcome measures and standard definitions for outcomes such as activity, remission and relapse in BS. The diversity and variability in measurement tools, outcomes and definitions of outcomes makes it difficult to compare the results of different trials.

One of the important questions is whether the organ-specific outcome measures developed and validated for other diseases and that have been widely used can be used to assess organ/organ system disease in BS, instead of trying to develop a new measure specific for Behçet's. An example to this was the use of standardisation of uveitis nomenclature (SUN) working group criteria that was used in a number BS studies. Recently The Ocular Behçet's Disease Research Group of Japan developed a new score that they called "Behçet's Disease Ocular Attack Score 24" to assess the severity of an ocular attack (8). The score consists of the assessment of 6 components: anterior chamber cells (maximum 4 points), vitreous haze (maximum 4 points), peripheral retinal lesions (maximum 8 points), posterior pole lesions (maximum 4 points), foveal lesions (maximum 2 points) and optic disc lesions (maximum 2 points). The tool showed good interobserver reliability among 5 uveitis experts who scored 50 ocular attacks from patient charts. There was a strong correlation between this score and general impression of the severity of attack on a 10 point visual analogue scale ( $r=0.926$ ,

$p < 0.0001$ ). They also showed that the score is sensitive to change, by assessing the score before starting infliximab and 6 months later in 150 patients with BS. How this scoring system performs in patients with different types of ocular attacks and how it correlates with visual acuity needs to be studied in larger number of patients. The performance in patients with different levels of chronicity and irreversible damage is another important issue.

Another effort regarding outcome measure research was the evaluation of reliability and validity of the Turkish version of BSAS, a patient reported outcome measure to assess disease activity among a group of 104 BS patients (9). The authors observed a good test-retest reliability (ICC=0.84, 95%CI 0.69-0.94), acceptable internal consistency (Cronbach's alpha 0.73, 95%CI 0.65-0.87) and moderate correlation with BDCAF ( $r=0.587$ ). BSAS scores did not appreciably change between men and women, older and younger patients and those with and without organ involvement. Although this seems to be surprising, it may be related to the fact that BSAS is not a measure of disease severity. Moreover it should be noted that there were relatively few patients with vascular (13/104), gastrointestinal (3/104) and neurologic involvement (1/104).

### Pathogenesis and genetics

Even though information about the pathogenetic mechanisms of BS is increasing, the real cause of this disease is still not clear. Both genetic and environmental factors are considered to play important roles in BS (10-12).

Among the environmental factors, the role of many infectious agents have been proposed. So far, many microbial infection hypotheses have been suggested with variable results, among which: 1) bacterial (*i.e.* the most investigated microorganism is represented by *Streptococcus sanguinis*); 2) viral; 3) heat shock proteins (HSP) (indirectly) and 4) molecular mimicry can be listed. It has been hypothesised that various microbial products, such as HSP, can participate in the immunopathological response in BS. HSPs rep-

resent a group of intracellular proteins which have the role of scavengers in the presence of other intracellular proteins and this occurs particularly during infections (13).

Several investigators have explored the role of *Helicobacter pylori* infection in the pathogenesis of BS (14-17). Recently, Lankarani *et al.* (18), found a high prevalence of *H. Pylori* and BS. However, they did not observe any statistically significant difference between *H. Pylori* infection and BS clinical profile and this is probably due to the small sample size recruited. Another emerging aspect in the field of environmental factors is represented by hepcidin, which is an antibacterial peptide found in human serum and urine. Cicek *et al.* (19) evaluated the serum and saliva samples of BS patients and recurrent aphthous stomatitis (RAS), and found lower levels of saliva hepcidin concentration in BS and RAS, than in controls. The authors thought that this reduced level of hepcidin could predispose patients to infection in the development of oral aphthae.

The human leukocyte antigen (HLA) class I allele, HLA-B\*51 represents the genetic factor with the strongest association with BS across different ethnicities. So far, it is not clear whether HLA-B\*51 as a molecule itself or linked to other genes, primarily contribute to BS susceptibility. Data from genome-wide association studies (GWAS) undertaken in Turkey and Japan showed that HLA-B\*51, HLA-A\*26, IL10 and IL23R-IL12RB2 are susceptible loci for BS (20-21). This year, a study group from China has also confirmed the association between IL10 polymorphism and BS (22); these results further emphasise the crucial role of IL-10 in BS initiation. Recently, Kuranov *et al.* (23), performed a study to test HLA association in HLA-B\*51 negative German and Turkish BS populations; the study results showed a significant association of HLA-Bw4-80I present on HLA-B\*51 as well as on other B-locus molecules with BS. This suggests that distinctive Bw4 epitopes on HLA-B locus molecules could play a role in BS pathogenesis. The study also indicates an association

with HLA-A\*26 in German and Turkish BS patients as a genetic risk factor independent from HLA-B\*51.

Ombrello *et al.* investigated the sources of BS risk within the MHC by directly ascertained and imputed SNP (single nucleotide polymorphism) genotypes along with HLA type and amino acid data in 1190 cases and 1257 controls (24). SNP mapping with logistic regression of the MHC identified the HLAB/MICA region and the region between HLA-F and HLA-A as independently associated with BS. HLA-B\*51, A\*03, B\*15, B27, B\*49, B\*57 and A\*26 contributed independently to BS, while rs116799036, a non-coding SNP upstream of HLA-B that was suggested to underlie the association of HLA-B\*51 with BS by Hughes *et al.* in 2013 (25), was not replicated. Instead, BS association was mapped to seven MHC class I amino acid residues, six around the peptide binding groove and one in the signal peptide. These residues are critical in defining the peptide-binding specificity of MHC-I molecules and they affect the engagement of MHC-I molecules by killer immunoglobulin-like receptors on natural killer and T cells. Furthermore, identification of a BS associated residue in the signal peptide of HLA-B independently links BS pathogenesis to cytotoxicity (24).

A genome-wide association study was performed among a Korean population of 379 BS patients and 800 controls to identify non-major histocompatibility complex susceptible genes. A replication experiment was performed in 363 Japanese patients and 272 controls (26). A novel association to the GIMAP (GT-Pases of immunity associated protein) locus was shown both in the original and the replication study, mapped to chromosome 7q36.1. A fine mapping study identified an association with four additional SNPs rs 1522596 in GIMAP4 (OR:1.45), rs10266069 and rs10256482 (OR 1.32 and 1.27) in GIMAP2 and rs2286900 (OR=1.61) in GIMAP1 areas. GIMAP plays a role in peripheral T-cell function as well as T-cell development and selection and influences T-cell apoptosis. GIMAP4 transcript levels in T lymphocytes of BS patients were significantly decreased when com-

pared to their levels in healthy controls, implicating a potential resistance to T-cell apoptosis and an abundance of Th1 related cytokines like IL-12 and IL-18 (26). To investigate whether this association was replicated in Europeans, a total of 1086 (326 patients and 760 controls) Spanish individuals were genotyped. The association between GIMAP and BS was not replicated in this cohort and there were no statistically significant differences among the patient and control groups either in the allelic or the dominant models (27).

The relationship between complement component C4 copy number variations and BS pathogenesis was investigated in a study from China involving 905 patients with BS, 205 patients with AS and acute anterior uveitis and 1238 healthy controls (28). Copy number variation analysis showed an increased frequency of more than 2 copies of C4A in BS patients (OR:2.84) and logistic regression analysis showed that it was an independent risk factor for BS in spite of the strong association with HLA-B51. A significantly increased expression of C4A and IL-6 was observed in the high copy number groups compared to the ones with a low copy number. The absence of these changes in patients with AS and the previously reported low copy numbers of C4A and C4B among patients with SLE, RA and Graves' disease implicate that copy number variations differ among immune-mediated diseases in humans (28).

miRNAs have been shown to play a critical role in the pathogenesis of auto-immune or auto-inflammatory diseases by influencing the control of proinflammatory cytokine production (29). SNPs may change the property of miRNAs through altering its expression and maturation. The association between common pre-mi RNA SNPs and BS, Vogt-Koyanagi-Harada (VKH) and ankylosing spondylitis associated anterior uveitis (AAU) was investigated in 859 BS, 400 VKH and 209 AAU patients and 1685 controls belonging to a Chinese Han population. Significantly increased frequencies of the miR-196a2/rs11614913 TT genotype and the T allele were found in BS patients (OR:1.63 and 1.45) but not in

VKH and AAU. A stratified analysis showed that rs11614913 TT genotype and the T allele were especially prominent in BS patients with arthritis (OR: 1.89 and 1.56). It was also determined that a functional variant of miR-196a2 conferred risk for BS but not for VKH or AAU by modulating the miR-196a gene expression and by regulating pro-inflammatory IL-1beta and MCP-1 production (29). The same group also investigated the association of miR-146A and Ets-1 gene polymorphisms with BS and VKH. miR-146a/rs2910164, rs57095329 and rs6864584 were genotyped in 809 patients with BS, 613 with VKH and 1132 normal controls and miR-146a and cytokine expression were examined in peripheral blood mononuclear cells. A decreased frequency of the homozygous rs2910164 CC genotype and C allele was determined in patients with BS compared to controls (OR 0.61 and 0.75) and IL-17, TNF-alpha and IL-1 beta levels were lower in CC cases. No effect of genotype was observed on IL-6 and monocyte chemoattractant protein-1 while IL-8 levels were slightly higher in CC cases. These changes were not prominent in patients with VKH (30).

A Korean group evaluated the genetic and non-genetic factors affecting the visual outcome of ocular BS among 77 patients with uveitis. Mainly non-genetic factors such as duration of uveitis, posterior uveitis, male gender, cataract and glaucoma were associated with a poor visual outcome. However HLA-B51 showed an association with near total blindness in those with posterior uveitis and HLA-A\*26:01 was strongly associated with posterior uveitis although it did not show any independent association with poor visual outcomes (31).

Another study from Korea employed targeted resequencing techniques to identify pathogenic genetic variants associated with BS uveitis. An enrichment kit was designed to capture whole exonic regions of 132 candidate genes in 32 samples of patients with severe BS uveitis and 59 normal controls (32). Five rare and 8 common single nucleotide variants were selected and the replication study was

performed in 61 cases and 120 controls. Several variants showed significant associations with BS uveitis (rs1801133 in MTHFR, rs1051790 in MICA, rs3966991 FCGR3A, rs5498 in ICAM1, rs199955684 KIR3DL3 and rs1051456 KIR2DL4) (32).

A systematic review and meta analysis examined the associations between thrombosis, ocular involvement and Factor V Leiden (FVL), G20210A prothrombin gene and C677T methyl tetrahydrofolate reductase mutations in BS (33). Twenty-seven studies were analysed. A significant association was found between the AA or GA genotypes of FVL polymorphism among patients with BS and the presence of any thrombosis (OR:2.51). This association disappeared when patients from Turkey were excluded; a factor probably related to the allelic heterogeneity of the mutation among different ethnic groups. No association was determined for the remaining mutations and eye involvement was also not related to any of these factors. The pathogenic significance of this finding is not clear since the current body of evidence considers that coagulation abnormalities do not explain the majority of thrombosis in BS (33).

TIRAP, a MyD88-adaptor-like molecule, has a regulatory role in Toll-like receptor-2 (TLR2) and TLR4 signalling; recently, the single nucleotide polymorphism (SNP) of TIRAP, which has been previously shown to be associated with BS in a European cohort, has not been replicated in either Turkish or Italian patients (34). Notably, a multicentre two-stage case-control study from China and The Netherlands has recently provided evidence that TLR2 gene is involved in the susceptibility to ocular BS (35). Moreover, the association of paraoxonase (PON L55M) gene polymorphism with BS has been investigated in a group of Turkish patients, concluding that PON L55M was significantly associated to BS patients; these data suggest that PON L55M also seems to play a role in the pathogenesis of the disease (36).

Recent genetic surveys have identified vitamin D receptor (VDR) as a susceptibility gene for several autoimmune diseases. A case-control study

from Tunisia (37) has recently been designed to investigate the association of VDR gene polymorphisms with BS and rheumatoid arthritis (RA), using polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP) techniques. The authors observed a significant association between TaqI polymorphism and BS in the elderly subjects. Moreover, the minor ApaI a allele tended to confer an increased risk for BS susceptibility. BS patients with VDR homozygous AA or aa genotypes were at increased risk for the development of erythema nodosum (EN) skin manifestation. Single nucleotide polymorphisms of the vitamin D family genes were investigated in another study in a group of patients with ocular BS (n=400), Vogt Koyanagi Harada syndrome (n=400), acute anterior uveitis with ankylosing spondylitis (n=218), paediatric uveitis (n=400) and healthy patients (n=600) in the Chinese Han population. The rs12785878 DHCR7 genotype TT and T allele were higher in ocular BS patients. No association was detected in the other groups and healthy controls (38).

A joint Portuguese-Iranian study combined a microarray study with a genome wide association study (GWAS) (39). The former was performed in 15 Portuguese BS patients and 14 matched controls whereas the latter was done in 976 Iranian patients and 839 controls. The microarray investigation found that the neuregulin signalling pathway was over-represented in patients with BS whereas the GWAS found a novel association with BS for rs6845297 located downstream of EREG (the epieregulin gene) and replicated three associations of NRG1 (the neuregulin gene) (rs4489285, rs383632 and rs1462891). The role of this pathway in BS pathogenesis is not clear.

The polymorphisms in the solute carrier family 22 member 4 (SLC22A4, SLC22A5) which were previously associated with inflammatory bowel disease and psoriatic arthritis, RUNX1 that can bind to SLC22A4 and JAK1, the downstream gene of RUNX1 were investigated in an association study involving 738 Behçet's patients with ocular involvement and 1873 healthy

controls, given the fact that HLA-B51 accounts for only 20% of the genetic risk in BS. Only JAK1 was associated with BS albeit with unknown functional significance (40).

Furthermore, an epigenome-wide study from US and Turkey was performed to investigate potential DNA methylation abnormalities in BS that might contribute to the pathogenesis of the disease (41). The results provided strong evidence that epigenetic modification of cytoskeletal dynamics underlies BS pathogenesis. This represents an interesting aspect that emphasises the potential of epigenetic studies to explore novel aspects of the pathogenesis of the disease. Another approach that has been proposed to study the immunological dysfunction in BS is the microchimerism. Alp *et al.* investigated the relationship between microchimerism and BS, by analysing the SRY gene (42); they observed that about 76% of BS patients and only about 4% of the healthy controls showed the presence of the SRY gene.

Increased serum levels of TNF in patients with active BS and the anti-inflammatory effects of the TNF- $\alpha$  inhibitors suggest a pivotal role for this cytokine in the pathogenesis. A recent meta analysis that involved 16 articles, 1708 patients and 1910 healthy controls assessed the association between TNF gene polymorphisms and BS (43). Significant associations were found between TNF-308 A/G (OR:0.73), TNF-238 A/G (OR:1.51), TNF-1031 C (OR:1.55) and TNF-857 T/C (OR:0.76). Stratification by ethnicity revealed that TNF-308 A/G and TNF-857 T/C were associated with BS in the Asian group while TNF-238 A/G and TNF-1031 C were related in the Caucasian group (43). The pathogenic implications of these polymorphisms are not clear.

Among the family of cytokines, there are several interleukins (IL) which are considered to act as mediators of inflammatory process in BS. Wang *et al.* (44) have recently investigated the expression of IL-27 in BS, finding that a decreased IL-27 expression is associated with active ocular involvement. Similarly, a decrease in the expression of IL-37 seems to be associated with ac-

tive BS (45), while elevated IL-33 levels were found to correlate with disease activity, particularly with neurological involvement (46, 47). Clinical activity in BS seems also to be associated with the up-regulation of IL-17 expression (48).

Moreover, a growing number of studies are exploring novel biomarkers for BD, such as analysing protein profiles of peripheral blood mononuclear cells (PBMCs). More specifically, Yoshioka *et al.* found the PBMC protein profiles, especially the profile of the 3 spots, would be useful candidate biomarkers for BD, discriminating inflammatory bowel diseases from BD and other diseases (49).

Finally, Ozyazgan *et al.* (50) examined the distribution of lectin-like oxidised LDL receptor-1 (LOX-1) levels in patients with active BS, evaluating the possible association of LOX-1 with the oxidised LDL (oxLDL), endothelial nitric oxide synthase (eNOS), nitric oxide (NO) and endothelin-1 (ET-1) levels. The results suggested that the endothelial dysfunction parameters are elevated in patients with BS having active disease; this represents an important measure that should be considered in terms of evaluating atherosclerosis risk in BS.

## Clinical manifestations

### Eye disease

Panuveitis and retinal vasculitis are among the major and more frequent manifestations of disease, occurring in 60–80% of patients, and often result in blindness over a few years if untreated (51).

Tugal-Tutkun *et al.* evaluated the sensitivity and specificity of uveitis specialists' interpretation of ocular photographs in diagnosing Behçet uveitis (52). For this purpose, Turkish uveitis specialists, blinded to the demographic and clinical features of patients, labelled ocular photographs as "Behçet uveitis: n=29" or "non-Behçet uveitis: n=30." Full agreement with the correct diagnosis was observed in 56–81%. The authors concluded that, there were ocular signs of Behçet disease such as smooth layered hypopyon, superficial retinal infiltrates with retinal haemor-

rhages, and branch retinal vein occlusion with vitreous haze that could be of pathognomonic importance for BS.

The prognosis of eye disease has improved in recent years. This has been reported by several authors so far (53, 54) and was also shown in a recent retrospective study by Chung *et al.* (55). The authors observed that the mean visual acuity was better among patients whose first visit was between 2004 and 2010, than those who registered between 1994 and 2000.

Kang and Lee evaluated the long-time progression of retinal vasculitis in BS patients using the fluorescein angiography (FA) scoring system (56). The authors suggested that the FA scoring system could be a useful tool to discern active inflammation from the quiescent phase.

#### Vascular involvement

A study from our group investigated the association and the timing of various vascular events among 882 BS patients with vascular involvement (57). Deep vein thrombosis of the legs was the most frequent vascular event (67%). The cumulative risk for recurrence of any vascular event was 38% at 5 years. Patients with extrapulmonary artery involvement were significantly older than those with venous and pulmonary artery involvement. There were significant correlations between dural sinus thrombosis and pulmonary artery involvement, Budd-Chiari syndrome and inferior vena cava syndrome.

Pulmonary artery involvement is mainly manifested by pulmonary artery aneurysms and solely by *in situ* pulmonary artery thrombosis (58). Varying and multiple pulmonary parenchymal lesions such as nodules, consolidations and cavities make up part of this involvement as well (55). This was similarly shown by Zhang *et al.* (59) in a retrospective survey of 14 BS patients with pulmonary manifestations. The authors noted that; compared to those with isolated parenchymal involvement (n=5), patients with pulmonary artery aneurysms (n=6) or isolated pulmonary artery thrombosis (n=3) had more frequent haemoptysis, extra-pulmonary vascular lesions and more severe prognosis.

#### Neurological disease

When the central nervous system is the primary affected site in an initial attack of BD, the differential diagnosis is particularly challenging (60, 61).

Noel *et al.* investigated the outcome of a large cohort of patients with neuro-Behçet disease (NBS) (62). They surveyed 115 patients (65 M/ 50 F) with exclusively parenchymal CNS involvement. 68% of the patients presented with acute course. Overall, 40% had severe disability at initial visit. After a median follow-up of 73 months, 29 patients (25%) became dependent or died. In addition to cyclophosphamide (CYP) (46%) or azathioprine (AZA) (35%) all 115 patients received corticosteroids. Patients receiving CYP were more likely to have longer event-free survival compared to those who were treated with AZA. The authors observed a relapse rate of 30% and a mortality of 10%, similar to that found in previous studies (63, 64).

Tunisian colleagues defined clinical characteristics of the 121 (78 M/ 43 F) NBS patients (65). The mean disease duration at the onset of BS was 6.4 years. While 61% had parenchymal (brainstem 21%, hemispheric 20%, spinal cord 2% and localisation not defined 18%) involvement, the remaining 39% had non-parenchymal involvement (meningitis 5%, dural sinus thrombosis 20% intracranial hypertension 9%, and arterial thrombosis 9%). As previously reported (63, 64) male gender and CNS parenchymal lesions were found to be associated with a poor prognosis.

Kikuchi *et al.* made quantitative analysis of the brainstem using MRI scans in patients with NBS (66) and found that *a.* the atrophy of the brainstem was an early (which appears as early as 2 years after the diagnosis) and specific finding for the diagnosis, and *b.* quantitative measurements of the brainstem atrophy were well correlated with the clinical symptoms as well as CSF levels of IL-6. However this important study lacks diseased controls.

Uygunoglu *et al.* investigated the microstructure of sleep in 30 patients with BS and in 44 age- and sex-matched healthy subjects (67). Patients with BS were divided as those with brainstem lesions and those with no neurological

involvement. When overall BS patients were compared to healthy controls, the sleep onset and the duration of superficial NREM sleep stage were found to be longer, the respiratory disturbance index along with the frequency of sleep apnea and restless leg syndromes were higher. However none of the parameters were found to be different when patients with neurological involvement were compared to those without. Tasolar *et al.* assessed whether vertebral artery involvement could be a probable cause in the ethiopathogenesis of NBS (68). They studied 45 patients with BS (with and without neurological involvement) and 29 healthy controls using Doppler USG. They observed some alterations in the vertebral arteries especially among those with NBS, but these observations were statistically non-significant.

#### Gastrointestinal involvement

Mucosal healing, defined as endoscopic complete resolution of all inflammatory and ulcerative lesions at during clinic remission, is a concept that has emerged as an important prognostic factor for inflammatory bowel diseases and has become an important endpoint in clinical trials with Crohn's disease and ulcerative colitis. Yim and colleagues surveyed the association of mucosal healing with a good prognosis at long term in BS patients with gastrointestinal (GI) involvement (69). They reviewed the charts of their patients with GI involvement and identified those who had a control colonoscopy, within 3 months after obtaining clinical remission. They compared the frequency of clinical recurrences among their patients who had and who did not have clinical remission during the control colonoscopy. Among their 80 patients who were in clinical remission, control colonoscopy showed mucosal healing in 23, whereas 57 patients still had active ulcers. During a mean follow-up of 10.5 (1–89) months, clinical recurrence was observed in 7/23 (30.4%) patients who had initial mucosal healing, compared to 39/57 (68.4%) patients who did not ( $p < 0.0001$ ). Multivariate analysis showed that active ulcers at endoscopy during clinical remission (absence of mucosal healing) and use of immu-

nomodulators during the maintenance of remission were factors that predict relapse. Similar to other inflammatory bowel diseases, mucosal healing seems to be an important prognostic factor for BS patients with GI involvement.

The same group also compared the long-term prognosis of their 276 BS patients with GI involvement and their 332 Crohn's patients followed between 1986 and 2010 (70). They observed that the frequency of surgery, postoperative clinical recurrence and admission to the hospital were similar among BS and Crohn's patients. The cumulative rate of surgery at 1 year, 5 years and 10 years were 17%, 29% and 36% among Crohn's patients and 20%, 32%, 44% among BS patients. On the other hand the frequency of corticosteroid use and immunosuppressive use were more frequent among Crohn's patients. The cumulative rate of corticosteroid use at the same time points were 40%, 64%, 77% among Crohn's patients and 25%, 43%, 59% among BS patient ( $p < 0.001$  for all time points). For immunosuppressive use, the cumulative rates were 22%, 49%, 66% among Crohn's and 12%, 27%, 38% among BS patients ( $p < 0.001$  for all time points). Although this difference seems to indicate a milder course in BS, requiring less corticosteroids and immunosuppressives, it may also reflect the tendency of clinicians to treat Crohn's disease more aggressively. It should be noted that 2/332 Crohn's patients had died during follow-up compared to 5/276 BS patients. The death was related to the disease in one of the Crohn's patients and 4 of the BS patients.

Paediatric onset is not frequent among BS patients. Paediatric patients may show some differences in the frequency of certain BS manifestations, when compared to adult patients. A small survey from Taiwan suggests that GI involvement may be quite frequent in paediatric BS patients (71). Among their 20 patients with paediatric BS who were followed between 1990 and 2010, 10 had GI symptoms and an endoscopy was performed in 5. All of these 5 patients had ulcers in the colon, terminal ileum and duodenum in 3 patients, oesophagus and pharynx in 1 patient and the antrum in the other patient. When

they compared their patients who were younger than 10 years to those who were at least 10 years old, they observed that gastrointestinal ulcers tended to be more common among the younger group (4/7 vs. 1/13,  $p = 0.015$ ). The authors suggest that paediatric BS patients with GI symptoms, especially those who are younger than 10 years, may deserve an endoscopic examination.

Japanese gastroenterology and rheumatology specialists published a consensus statement for the management of intestinal BS (72). They suggest to use mesalazine (5-ASA) for patients with mild to moderate activity. For patients with severe symptoms they suggested induction therapy with corticosteroids and TNF-alpha antagonists (adalimumab or infliximab). They recommend the use of immunosuppressive agents such as azathioprine in corticosteroid dependent, corticosteroid resistant or TNF-alpha antagonist resistant patients. This is somewhat different from the usual practice in some other parts of the world, where TNF-alpha antagonists are usually reserved for patients who have failed azathioprine (73).

#### *Fever*

The frequency of recurrent fever episodes was investigated in 500 BS patients along with diseased (SLE:  $n = 72$ , FMF:  $n = 94$ , AS:  $n = 100$ ) and healthy controls ( $n = 100$ ) (74). History of fever episodes was present in 22% patients with BS, 87% with FMF, 33% with SLE and 8% with AS. Among BS patients, patients with vascular involvement had increased risk for having fever episodes when compared to patients with solo skin-mucosa lesions [OR: 4.0 (95% CI: 2.1–7.5)  $p < 0.001$ ].

#### *Pregnancy*

A previous survey from France reported on the favourable outcome of 76 pregnancies in 46 patients with BS (75). The disease course of BS also seemed to be good during pregnancy. This time, in a retrospective survey, Iskender *et al.* investigated 49 pregnancies in 24 patients with BS (76). 147 healthy women who delivered at the same institution were selected as the controls. In BS, during pregnancy, 91% either had no symp-

toms at all or had no change while the remaining 9% had relapses. Vascular complications were observed in 2 patients. The rates of stillbirth, pre-eclampsia, preterm delivery, intrauterine growth and perinatal mortality did not differ between patients and controls.

#### *Malignancy*

Lin *et al.* described 41 BS patients with malignancies (77). 29 cases developed haematologic malignancies (myelodysplastic syndrome being the most common), while 12 remaining developed solid neoplasms (colorectal cancer being the most common). Female gender, older age and gastrointestinal tract involvement were more frequently observed among patients with malignancy. Exacerbation of BS during the emergence of malignancy was more frequently observed among patients with haematologic malignancies.

#### *Depression and personality traits*

Yetkin *et al.* investigated depression and sexual dysfunction using Female Sexual Function Index (FSFI) and Beck Depression Inventory (BSI) scales (78). They studied female BS patients with solo skin-mucosa lesions and age- and sex-matched healthy subjects. They showed that depression and female sexual dysfunction were more common in BS patients when compared to healthy controls. In a similar study, Atay *et al.* examined the personality characteristics of BS patients using the Temperament and Character Inventory (79). Interestingly, BS patients were found to be materialistic, self-contained, self-confident, cold, and reserved although not shy when compared to healthy controls. The authors suggested that this may have a positive impact on quality of life and comorbid major depressive disorder.

#### *Atopy*

Yazici *et al.* observed that the frequency of atopy was significantly lower in BS (2%) and in FMF patients (5%) when compared to healthy controls (16%) (80).

#### *Reviews*

A comprehensive review on NBS by Saip *et al.* (81), a concise review on BS

with emphasis on dermatological complications by Mat *et al.* (82), a review on HLA-B51 and the risk of BS by Graham Wallace (83) and, very recently, recommendations for the key issues in the diagnosis and management of NBS by an expert committee (84) have been published.

### Management

#### *Colchicine at long term*

Colchicine is frequently chosen as the first line treatment of mild mucocutaneous and joint manifestations of BS. However, it is, not known whether continuous use of colchicine decreases the development of organ involvement at the long term. In a recent survey, we looked at the long-term prognosis of 116 patients who had taken part in a 2 year, double blind, placebo-controlled trial of colchicine (85). These patients had early disease with only active mucocutaneous manifestations when they had entered the trial a mean of 16.6 years ago. Outcome information obtained in 90 patients (78%) showed that 31% of patients had developed organ involvement necessitating the use of immunosuppressives during the post-trial period with half of them being from the colchicine arm. There was no statistically significant difference regarding the use of immunosuppressives among patients who continued to take colchicine during the post-trial period (34%) compared to those who did not (25%). The cumulative duration of colchicine usage was also not different between patients who received immunosuppressives and those who did not. These data suggest that colchicine, even when initiated at early stages of the disease and continued afterwards, does not seem to decrease the necessity of immunosuppressive treatment as an indication of major organ involvement at the long-term. The small numbers of the patients evaluated in this study still leave the gate open for a prospective, controlled, withdrawal study among colchicine responders.

#### *TNF- $\alpha$ inhibitors for intestinal involvement*

In a multicentre study from Korea, 28 BS patients with active and refractory intestinal involvement have been treat-

ed with infliximab at a dose of 5 mg/kg (86). Sixteen patients (57%) received regular scheduled infusions of infliximab while the remaining 12 (43%) received infliximab only on relapse. High clinical response rates were observed initially which tended to decrease afterwards. Fifteen patients (53.6%) achieved sustained response during a median follow-up of 29.5 months. Older age ( $\leq 40$  years) at diagnosis, female sex, long ( $\geq 5$  years) disease duration, concomitant immunomodulator use and achievement of remission at week 4 were found to be predictive factors for sustained response. Ulcer shape, the type of infliximab infusions (scheduled versus on demand), CRP normalisation and previous history of surgery had no impact on the response to infliximab. One patient developed gastrointestinal sepsis requiring surgical resection after 16 weeks of infliximab therapy. The second study from Japan reported 15 patients out of a cohort of 43 BS patients with intestinal involvement that have been treated with infliximab at a dose of 5mg/kg in a single centre (87). All patients had active gastrointestinal symptoms despite treatment with conventional medications (azathioprine, 6-mercaptopurine, prednisolone, colchicine and 5-aminosalicylic acid) and 4 of them also had fulminant disease defined as having severe abdominal discomfort or extensive gastrointestinal bleeding requiring immediate therapy to prevent emergency surgery. The median follow-up after the initiation of infliximab was 100 weeks. Evaluation of the patients at 10 weeks after initiating infliximab showed a response rate of 80% with 8 patients (53%) achieving clinical remission (complete disappearance of the GI symptoms and normal CRP level) and 4 patients (27%) having a clinical response (improvement of GI symptoms with decreased CRP levels). The 3 non-responders were among the 4 patients with fulminant disease. Two of them underwent surgery and one responded to high dose corticosteroids. The response rate to infliximab was 64% at 12 months and 50% at 24 months. The cumulative probability of recurrence was 20% at week 10, 29% at month 12 and 51% at month 24. Fulminant intestinal disease

at the initiation of infliximab therapy was predictive for failure to infliximab at week 10. Contrary to the findings in the Korean study, the duration of intestinal involvement and concomitant use of azathioprine were not related to the clinical response. These two studies indicate that infliximab may be a good choice for refractory intestinal involvement of BS.

#### *Stopping TNF- $\alpha$ inhibitors in uveitis*

Despite the lack of formal controlled studies, TNF- $\alpha$  inhibitors and especially infliximab are accepted as being effective in the treatment of severe and refractory uveitis of BS. However, the clinical course of uveitis after cessation of infliximab in responders is unknown. A recent retrospective study from Saudi Arabia on 19 BS patients with refractory uveitis provides some data on the clinical course of uveitis following withdrawal of infliximab after achieving sustained remission (88). In 9 patients infliximab was stopped following sustained remission. The mean number of infliximab infusions in these patients was 30 (between 13–43 infusions) and the duration of infliximab treatment was 56 months (22–87 months). Four of these 9 patients flared after an interval of 3–10 months following cessation of infliximab and the remaining 5 maintained their remission during a mean period of 25 months (19–31 months). Two of these 5 patients also discontinued their concomitant immunosuppressives but the remaining 3 continued to take them in reduced dosages.

Another retrospective study from Japan investigated the clinical course of uveitis among 7 BS patients who discontinued infliximab treatment either because of lack of efficacy (1 patient) or due to adverse events (6 patients) (89). Adverse events leading to withdrawal of infliximab in 6 patients were bacterial pneumonia, miliary tuberculosis at the 3. month of treatment, infusion reaction, development of psoriasis, elevation of liver transaminases and leukopenia, respectively. Five of the 7 patients were in complete remission under infliximab (mean 11 months, range: 1–25 months). Following discontinuation of infliximab 6 patients received their previous therapies consisting of predniso-



lone (2 patients), cyclosporine A (2 patients), and colchicine (2 patients). The decrease in the frequency of uveitis attacks under infliximab was maintained up to 24 months after discontinuation. The mean visual acuity did not change significantly after withdrawal of infliximab. Taken together, the results of these two retrospective studies suggest that withdrawal of infliximab may be considered in patients achieving clinical remission of uveitis.

#### *Endovascular treatment of aortic aneurysms*

Arterial involvement of BS often necessitates invasive interventions in addition to drug therapy in the management of patients. The development of aortic pseudoaneurysms is an important complication of BS that has a high mortality rate if rupture occurs. Surgery can be complicated by anastomotic dehiscence and development of pseudoaneurysms at the anastomosis sites. A retrospective study from a single centre in Korea investigated the long-term outcome of 10 BS patients (8 men) who underwent endovascular stent grafting for aortic pseudoaneurysm (90). The total numbers of pseudoaneurysms were 12, with 7 being in the infrarenal abdominal aorta, 4 in the descending thoracic aorta and 1 in the aortic arch. Five of these patients had also aneurysms or arterial occlusion at other sites. There were no technical problems or immediate complications during the procedures. Median duration of follow-up was 57 months. Imaging studies showed complete resolution of the aortic pseudoaneurysms in all patients. One patient with an abdominal aortic pseudoaneurysm developed a new pseudoaneurysm at the distal margin of the stent graft 17 months following the procedure but did not require any further intervention during follow-up with serial imaging for 5 years. A second patient with pseudoaneurysm of the descending thoracic aorta required a further intervention for a pseudoaneurysm of the left subclavian artery during follow-up. Nine patients received immunosuppressive therapy with steroids and azathioprine before the intervention, which was maintained during follow-up. In summary, the complication

rate in these series of patients was low with only one patient developing a new pseudoaneurysm at the distal margin of the stent graft that did not require any further intervention. The authors underlined the importance of early initiation of immunosuppressive therapy before the interventions and maintaining this therapy during follow-up in reducing post-operative complications.

#### *Intravitreal treatment*

A retrospective study from Korea reported the experience with fluocinolone acetonide intravitreal implant in the treatment of refractory uveitis of BS (91). This implant, which has been approved for the treatment of chronic noninfectious uveitis, enables local steroid release into the eye over a 3-year period. The implant was applied to 8 eyes of 7 BS patients. During a mean follow-up of 48 months, visual acuity improved by more than 3 lines (Snellen chart) in 6 of the 8 eyes. Five patients could discontinue all systemic medications. Elevations of intraocular pressure requiring glaucoma shunting surgery (5 patients) and post-operative cytomegalovirus endothelitis (1 patient) responding to antiviral therapy without removal of the implant were the major complications. Another retrospective study from the same center in Korea reported the long-term effects of intravitreal triamcinolone acetonide injection in 49 eyes of 49 BS patients with refractory uveitis (92). The mean duration of follow-up after the injection was 55 months. Complete control of inflammation was observed in 87% of the patients but 60% of them relapsed within 1 year following injection. Repeated injections were required for 15 eyes (31%) within 2 years following the first injection. On the other hand, it was possible to stop or to reduce systemic medications in 24 patients (49%). Elevation of intraocular pressure was observed in 41% of the treated eyes. The results of both studies suggest that intravitreal steroid implants or injections may have some place in the treatment of patients with uveitis, who are refractory to or could not tolerate systemic medications. Potential side effects of these therapies need special attention.

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