

# Behçet's syndrome: a critical digest of the 2012-2013 literature

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### ABSTRACT

Recent work on the epidemiology of Behçet's syndrome confirm the previous contention that the prevalence increases from North to South and that the disease follows a more severe course in patients with an early age of onset, also when specifically studied in patients with eye and gastrointestinal involvement. Imputation analyses of genome wide association studies revealed new associations such as *ERAP-1*, *CCR1-CCR3*, *KLRC4* and *STAT4*. Further work suggested that the BS associated variant of *STAT4* is not related to the previously reported one associated with autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus. The prognosis of eye involvement seems to have improved over the last decade with better visual acuity and less frequent severe complications in patients reported in the 2000s compared to the 1990s. Immunosuppressives and corticosteroids were observed to improve the outcome of cardiac involvement in BS. Recurrence and complications were common in these patients when surgery was performed without immunosuppressives. The cognitive dysfunction in BS patients with neurological involvement seemed to be severely impaired and worse than that of multiple sclerosis patients, suggesting a more severe "frontal"-executive dysfunction. Gastrointestinal involvement seemed to be brought to a remission in the majority of BS within 5 years, with about one fourth of the patients following a relapsing or chronic disease course. *TNF- $\alpha$*  inhibitors have become standard treatment for patients resistant to conventional immunosuppressives. Switching to another biologic can be effective when the first or even the second biologic agent fails or is stopped due to adverse events.

### Introduction

Behçet's syndrome (BS), a multisystem vasculitis that is still considered an orphan disease in many parts of the world, have been attracting increasing attention from researchers. A recent scientometric analysis of articles on BS showed that the number of articles published each year has been constantly increasing, from 97 articles in 1990 to 573 articles in 2010 (1). The number of articles published from each country somewhat echoes the prevalence of BS in that country, Turkey followed by Japan being the 2 most frequently publishing countries on BS. In this review we aimed to bring together most recent research on different aspects of BS, based on manuscripts mainly published during 2012 and 2013.

### Epidemiology

The most common comment on the prevalence of BS is that it is more prevalent along the ancient Silk Route. However, until now there had been few reports on BS from countries lying to the South of the Silk Route. There have been 3 reports from such countries during the previous year: India, China and Taiwan (2-4).

In the report from China, 334 patients (195 men, 139 women, mean age 35.8±11.1 years) with BS who were followed in rheumatology departments were reported (2). Among these patients 17.3% were HLA B51 (+). The authors noted that 4 out of every 100 patients seen in their clinic had BS and estimated the prevalence of BS in the general population of China as 14/100,000. This is lower than the previously reported prevalence in China by Kaneko *et al.* which was 120/100,000 (5). Regarding their clinical manifestations, in addition to the skin and mucosa findings, 28% of the patients had joint, 26% had eye, 17% had vascular, 17% had gastrointestinal, 10% had nervous, 8%

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had cardiovascular and 5% had pulmonary involvement. These patients had more severe disease with more major organ involvement compared to those in the previous report. The authors attributed this to the fact that theirs was a referral centre, accepting the more complicated cases. The report from India included 29 BS patients (6 men, 23 women, mean age at disease onset 27.4 years) followed in the dermatology department of University of Delhi (3). These patients mostly had mucocutaneous and joint involvement, with 31% eye involvement, 3.4% gastrointestinal involvement and no vascular or neurologic involvement. This may be because this series is coming from a dermatology clinic. The report from Taiwan is a population based study of the prevalence, incidence and mortality rates of rheumatic diseases, based on the longitudinal health insurance database of the Taiwan National Health Insurance which covers 99% of the population (4). According to this study the prevalence of BS is 1.4/100,000 (95% CI 0.4–2.3), and the incidence rate is 0.8/100,000. These were lower than the prevalence and incidence rate of other rheumatologic conditions in this population. The mortality rate is reported as 1,144.4 per 100,000 person-years and the standardised mortality ratio (SMR) of BS as 3.7 (95% CI 1.2–11.6). The SMR for men only was 2.0 (95% CI 0.3–14.4), lower than all of the other rheumatologic conditions that were studied in this population.

A generally accepted finding is that the prevalence of BS increases as one goes from North to South. A recently published prevalence study from southern Italy by Olivieri *et al.* is also in line with this contention (6). They surveyed a population of 69,060 subjects living in Potenza and identified 13 patients with BS. Eleven of these fulfilled International Study Group (ISG) criteria giving a prevalence of 15.9/100,000 (95% CI 8.9–28.5). This was higher than the only other population based prevalence study coming from Reggio Emilia, in the north of Italy, reporting a prevalence of 3.8/100,000 (7). Interestingly the frequency of HLA B51 positivity was similar in these 2 stud-

ies, 19% in the Reggio Emilia study and 17% in the Potenza study. Another study from Europe aimed to determine the incidence, prevalence and clinical characteristics of BS patients from southern Sweden (8). Mohammed *et al.* reported a point prevalence of 4.9/100,000 and an annual incidence rate of 0.2/100,000. The prevalence reported here is higher compared to the previous report from Sweden which was estimated as 1.18/100,000 (9). This was explained by immigration from BS prevalent areas. When they analysed the prevalence according to ancestry, it was significantly higher among the population with non-Swedish ancestry (13.6 vs. 2.0/100,000,  $p < 0.001$ ). Among the 40 BS patients they had identified (27 men, 13 women, median age at diagnosis 30.5 years), 70% were of non-Swedish ancestry. Another interesting point is that the men to women ratio was 3.66 among patients with non-Swedish ancestry whereas it was 0.71 among patients with Swedish ancestry. The clinical features were not different between patients of Swedish and non-Swedish ancestry, overall 53% had eye involvement, 40% had joint involvement and 20% had venous thrombosis. Another report from the north of Europe was the paper by Gyldenlove *et al.*, reporting a low prevalence of pathergy positivity among BS patients from Denmark (10). Among the 26 BS patients followed in the rheumatology department of Rigshospitalet, only 2 (8%) had a positive pathergy reaction. One of these patients was of Turkish and the other of Iranian origin. Among the 9 patients with Danish origin, none had a positive pathergy reaction.

Apart from the wide variation in prevalence, the frequency of various manifestations is also known to show variation between different geographies. This is evident from several series of BS patients reported from different countries. An interesting paper shows this finding from a different aspect, from an ophthalmologic point of view. Nashtai *et al.* have compared the patterns of uveitis in the middle East and Europe by a literature review (11). BS was the second most frequent cause of uveitis in the Middle East (including

Turkey) making up 18% of the cases, whereas only 3% of all uveitis cases was related to BS in Europe. Results were similar when anterior uveitis and posterior uveitis cases were compared separately. However BS was the most common identified cause of panuveitis in both the Middle East (45%) and Europe (18%). Another study related to uveitis was by Saleh *et al.*, reporting clinical presentation and course of BS uveitis in patients followed at the University of Illinois, with and without an ancestry of Silk Route countries (12). Among their 6134 patients with newly diagnosed uveitis, 101 had BS. They included 36 of these patients, those who fulfilled ISG criteria and had complete medical records. Among these, 10 had Silk Route ancestry (6 from Asia, 2 from Saudi Arabia and 2 from North Africa). The types of ocular findings were similar between patients with Silk Route and non-Silk Route ancestry. Retinal vasculitis was the most common type of involvement (86%) followed by panuveitis (75%), retinitis (33%) and hypopyon (22%). This is somewhat different from reports of BS uveitis from other parts of the world where panuveitis is the most common finding. The response to treatment and complications were also similar among Silk Route and non-Silk Route origin patients, with cataract being the most common complication.

Another well established epidemiologic concept in BS is the more severe disease course among younger onset and male patients (13). Two recent papers were published dealing with this concept specifically among BS patients with uveitis and gastrointestinal involvement. Hazirolan and colleagues identified 26 patients with onset after the age of 40 among their cohort of 1130 BS patients (14). Fourteen of these patients (54%) had uveitis, but this was in the form of anterior uveitis except for 2 patients who had panuveitis. This was interpreted as milder eye involvement with better prognosis in late onset BS patients. The other study is on the effect of age of onset and sex on gastrointestinal involvement. As will be discussed in more detail in the clinical manifestations section of this

manuscript, Jung *et al.* have reported a more severe course and poorer prognosis among patients with a younger age at onset (15). However, in contrast to what is known for other manifestations of BS, the outcome of gastrointestinal involvement was not worse among men compared to women. Finally, in one study that sought to determine whether the number and frequency of mucocutaneous manifestations at disease onset influence the disease course at long term, the outcome of BS patients who were randomised to the placebo arm of the randomised controlled thalidomide study which included male patients with only mucocutaneous involvement were re-evaluated after a mean of 11.7 years (16). Half of these patients had developed major organ involvement over the years during the post-trial period. ROC curve analysis was used for identifying predictors of major organ involvement requiring immunosuppressive use in this group and showed that having at least 10 ulcers during 6 months had a sensitivity of 86.7% and a specificity of 53%. Thus, it was suggested that frequency of oral ulcers during the initial years of disease may predict the development of major organ involvement requiring immunosuppressives in men with BS.

### Pathogenesis

The currently accepted concept regarding BS pathogenesis is that an appropriate genetic background leads to an innate immune system driven activation sustained by adaptive immune responses to environmental factors such as infections and auto-antigens (17). Among the genetic factors, HLA-B51 confers the strongest association and has been replicated in many populations (18). Genome wide association studies (GWAS) have suggested additional susceptibility loci. Remmers *et al.* and Mizuki *et al.* had previously shown that variants in the major histocompatibility complex (MHC) class I locus, IL-10 and IL-23R were associated with BS in Turkish and Japanese populations (19, 20). An imputation analysis done by the former group that increased the number of single nucleotide polymorphisms (SNP) to

779465 in 1209 BS cases and 1278 controls and in Japanese and Turkish replication cohorts revealed new associations. ERAP-1 had an odds ratio (OR) of 4.56 (2.88-7.22) in the meta-analysis of Turkish discovery and replication populations and was more prevalent in HLA-B51 positive individuals compared to B51 negatives. This suggested an epistatic interaction between the two genes. It codes an endoplasmic related aminopeptidase that trims peptides and loads them to Class I MHC molecules and shows that peptide-MHC class I interactions are important in the pathogenesis. Similar interactions also play a role in ankylosing spondylitis and psoriasis, suggesting shared pathogenic mechanisms among the three conditions. Other loci that reached genome wide significance involved CCR1-CCR3 (a cluster of chemokine receptor genes), KLRC4 (a natural killer cell receptor gene) and STAT4 (signal transducer and activator of transcription 4). CCR1 expression and monocyte chemotaxis were reduced in patients carrying the disease risk allele which showed that impaired clearance of pathogens may contribute to pathogenesis in BS. KLRC4 is within a haplotype block containing five NK receptor genes and encodes a C-type lectin receptor with an unknown function. It is speculated that it acts as a costimulatory molecule for CD4<sup>+</sup> and CD8<sup>+</sup> cells and MICA (MHC class I chain-related protein A) is one of its targets. The BS associated variant of STAT4 is not related to the previously reported autoimmune disease associated variant seen in rheumatoid arthritis and systemic lupus erythematosus (21). A GWAS performed in a Han Chinese population showed the same relationship for STAT 4. It was additionally suggested that STAT 4 regulated the production of IL-17 by increasing its m-RNA and protein levels in individuals carrying the rs897200 risk genotype AA. The clinical disease severity score was also higher in individuals who carried this genotype (22). This is in line with the recently described role of IL-17 in BS. A Spanish group evaluated the STAT 3 rs744166 polymorphism among a group of patients with psoriatic

arthritis and BS. The polymorphism was related to psoriatic arthritis but not to BS (23).

Kirino *et al.* did a targeted re-sequencing study among patients with BS to determine rare and low frequency genes. They used three different burden tests to increase the power of the study and included genes related to autoinflammation which were not shown in any previous GWAS. They found variants of IL-23R, IL1R1 and TLR and NOD2 among the Japanese and IL-23R (different from the one found in the Japanese cohort), TLR4, MEVF (M694V) and NOD2 (again different from the one found in Japanese) among the Turkish. One hundred and seventy eight patients among 1933 with Turkish BS and 67/1872 controls carried the M694V allele without another exon 10 mutation. The different NOD2 variants found among the Japanese and Turks were related to the discrepancy in the frequency of intestinal involvement among the two populations (24).

Amr Sawalha and colleagues performed dense genotyping of the HLA extended locus by imputation based association mapping in a cohort of 503 Turkish individuals with BS and 504 controls and 144 Italians with BS and 1270 controls. Genotyped SNP's were used to infer classical HLA alleles in the HLA-A, B, C, DQA1, DQB1 and DR-B1 loci. They suggested that the HLA-B51 association in BS was explained by a variant located between the HLA-B and MICA genes (rs116799036, OR=3.88). They also claimed that the genetic association with HLA-B51 completely disappeared when controlling for a SNP located 24 kb upstream of HLA-B and 18 kb upstream of MICA, suggesting that HLA-B51 is likely not causal. Three additional independent genetic associations within PSORS1C1 (rs12525170), upstream of HLA-F-AS1 (rs114854070) and with HLA-Cw\*1602 were also identified and replicated. No association was observed with MHC class II alleles (25).

Candidate gene approaches were done for CC chemokine receptor 5 (26), TNAIP3 (27), DD genotype of ACE gene I/D (28), Rho-kinase (ROCK 2) (29), macrophage migration inhibi-

tory factor (30), PDGFRL (31), CCR1-CCR3 (32) and MDR1 (33) polymorphisms with varying results, but the findings are not robust due to low power.

Apart from the genetic studies, recent studies delineating the role of innate and adaptive immune systems were also published. One of these, is the study by Parlakgul *et al.* that evaluated the activation status of  $\gamma\delta$  T cells, which are thought to bridge the innate and adaptive immune systems and which were reported with conflicting results in the peripheral blood of BS patients in previous studies (34). The NKG2A, NKG2C, NKG2D, CD16 and CCR7 molecules on  $\gamma\delta$  T cells of active and inactive BS patients as well as active tuberculosis patients and healthy individuals as controls were studied. They also measured the cytokine production after expanding peripheral  $\gamma\delta$  T cells with a phosphoantigen and IL-2 and restimulating with BrHPP and a TLR3 ligand. They observed low levels of  $\gamma\delta$  T cells in BS and tuberculosis patients and healthy controls. However the proportions of TCRV $\delta$ 2<sup>+</sup> T cells were lower among BS patients and tuberculosis patients compared to healthy controls (58.9%, 50.7%, 71.7% respectively,  $p=0.04$  and 0.005). And the proportions of CD16<sup>+</sup> and CCR7<sup>+</sup> TCRV $\delta$ 2<sup>+</sup> T cells were higher among BS and tuberculosis patients (26.2%, 33.9%, 16.6%,  $p=0.02$  and 0.001 respectively and 32.2%, 27.9%, 17.7%,  $p<0.0001$  and  $p=0.014$  respectively). A difference in the expansion capacity of  $\gamma\delta$  T cells was observed with a lower expansion capacity in BS and tuberculosis patients and lower IL-13, IFN $\gamma$ , GM-CCSF, TNF- $\alpha$ , CCL4 and CCL5 production in response to TLR3 ligand and BrHPP restimulation in BS patients compared to healthy controls. These functional changes of  $\gamma\delta$  T cells despite no increase in the proportion of  $\gamma\delta$  T cells were interpreted to implicate that  $\gamma\delta$  T cells have already been exposed to regulatory effects in BS and tuberculosis patients causing a change in their activity.

In a study aiming to delineate the mechanisms of innate immune responses in BS patients, Ture-Ozdemir

*et al.* studied inflammasome activation in dendritic cells and neutrophils of BS patients with active mucocutaneous lesions and healthy controls by stimulating with pattern recognition receptors (retinoic acid-inducible gene 1 – like receptors and nucleotide-binding oligomerisation domain – like receptors) and determining the caspase-1 and pro-inflammatory cytokine responses (35). They did not observe a difference in inflammasome formation in response to stimulation with pattern recognition receptors among BS patients compared to healthy controls. Only a slightly defective activation of dendritic cells of BS patients in response to nucleotide-binding oligomerisation domain 2 stimulus was observed. It was suggested that activation of inflammasomes through caspase-1 does not seem to be predominant in BS. It should be kept in mind that these were only mucocutaneous BS patients without eye, vascular, neurologic or gastrointestinal involvement. Considering the hypothesis that different pathogenetic mechanisms may be operative in different types of BS involvement (36) the applicability of these results to BS patients with other types of involvement needs to be studied. As the authors suggest, whether caspase-1 independent pathways such as toll-like receptors play role in innate activation in BS, also needs to be further studied.

Two recent papers by Bang's group, looked further into the role of *Streptococcus sanguinis*, the most frequently hypothesised pathogen, in the pathogenesis of BS (37, 38). The first one aimed to identify by proteomics analysis an anti-*Streptococcus sanguinis* antigen that reacts with serum IgA antibodies in BS patients (36). A *Streptococcus sanguinis* GroEL protein targeted by serum IgA antibodies of BS patients was identified. Moreover it was observed that BS patients showed serum IgA reactivity against homologous epitope regions between this GroEL and human heterogenous nuclear ribonucleoprotein A2/B1. It was suggested that an infectious trigger may be activating autoreactive lymphocytes by recognising these homologous epitope regions. In the other study, membrane expression

of  $\alpha$ -enolase in human dermal microvascular endothelial cells (HDMECs) were studied in a small number of samples. It was observed that membrane expression of  $\alpha$ -enolase in HDMECs was stimulated when cultured with *Streptococcus sanguinis* and also the sera of active BS patients in a dose-dependent manner. Earlier and higher expression was observed with sera from BS patients compared to healthy controls. The authors suggest that this membrane expressed  $\alpha$ -enolase might react with anti- $\alpha$ -enolase antibodies in BS sera resulting in increased inflammation and endothelial cell destruction.

## Clinical manifestations

### Eye disease

The prognosis of eye disease has improved in recent years. Yoshida *et al.* had first noticed an improvement of disease course and visual outcome in the 1990s compared to the 1980s in Japanese patients with Behçet uveitis (39). Similarly, Tugal-Tutkun *et al.* had reported that the risk of losing useful vision was lower in patients who presented in the 1990s than in patients who presented in the 1980s (40). In a recent study, the same group compared clinical characteristics and 3 year outcome of BS patients with uveitis presented in the 1990s ( $n=170$ ) and 2000s ( $n=258$ ) (41). There was no significant difference in the demographic features, including age at presentation, age at onset of uveitis, disease duration, and gender. Panuveitis was significantly less common, visual acuity was better, and more patients received immunosuppressive treatment prior to presentation, in the 2000s. There was no significant difference in the number of uveitis attacks in the first 3 years, however, useful vision loss and severe ocular complications were fewer in the 2000s.

### Vascular disease

Shin-Seok Yang *et al.* reviewed the clinical characteristics and vascular interventions of 28 BS (24 M/ 4 F) patients with peripheral arterial involvement out of 1059 BS patients followed between 1995 and 2010 (42). Twenty-eight patients had 54 arterial lesions such as aneurysms ( $n=30$ ), occlusions

(n=20) and stenoses (n=4). The most commonly involved arteries were femoral, popliteal and iliac arteries. A total of 21 patients underwent 28 interventions either endovascular (n=10) or surgical (n=18). Only 18 patients received immunosuppressive treatment. There were 10 relapses and 1 death during a follow-up period of  $78.7 \pm 52.5$  months. Authors attributed the relapse risk to the delay in diagnosis and being treated without immunosuppressives. Endovascular interventions were in general successful. Surgical interventions were mainly synthetic graft interpositions (n=10) and bypass (n=8) procedures. Ligation was the least preferred method. The complication rate with autologous vein grafts was found to be similar when compared to that with synthetic grafts. This complication however was substantially high in the series reported by Tuzun *et al.* (43). A Chinese group reviewed the clinical characteristics of 20 patients (17 M/ 3 F) with cardiac involvement out of 405 (260 M/ 145 F) BS patients admitted between 1996 and 2011 (44). Thirteen had aortic valve involvement with severe aortic regurgitation and 7 had intracardiac thrombus (right side: n=4, left side: n=1, both right and left side: n=2). Diagnosis of BS was delayed 1 to 24 months in eleven (85%) patients because patients did not fulfill the ISG criteria for BD at the onset heart failure. The outcome of patients treated with prednisone and immunosuppressives was good: the intracardiac thrombus disappeared or decreased in 5, remained stable in 2, while the heart failure disappeared in all patients with aortic involvement. On the other hand, surgery alone did not lead to complete resolution since 5 of the 8 patients underwent a second operation due to recurrence of thrombus or valvular dehiscence / leakage.

A South Korean group evaluated post-operative complications in 41 BS patients who had undergone cardiovascular surgery between 1990 and 2009 (45). Fifty-nine operations were performed in 41 patients. The indications for operation were valvular dysfunction, arterial aneurysm, arterial or graft occlusion, fistula and cardiac anomaly.

During the mean follow-up period of  $65.3 \pm 48.1$  months, complications such as paravalvular leakage, dehiscence, fistula, graft occlusion, or pseudoaneurysm occurred in 29 operations (49.2%). Post-operative immunosuppression was found to independently lower the risk of complications.

#### *Neurological involvement*

Talarico *et al.* studied the clinical characteristics BS patients with neurological involvement followed between 1989 and 2009, by a single centre in Italy (46). Neurological involvement was observed in 38% (44/117 patients, 36 M/ 8 F), indicating a considerably higher prevalence of neurological involvement compared to the previous literature. Authors attributed this to the hospital-based nature of their cohort. The mean age of the patients was  $42 \pm 9$  years, although their age at disease onset was  $25 \pm 4$  years. There were ischaemic pontomesencephalon lesions in 19 patients, meningoencephalitis with brainstem involvement in 16, peripheral nervous system involvement in 4 and cerebral venous thrombosis in 2. The most common presenting symptoms were listed as headache, behavioural changes, hemiparesis, pyramidal signs, sphincter disturbances, meningeal signs, hearing loss, seizures and optic neuropathy. As it has been previously shown (47) neurological involvement was a late complication appearing mostly (31/44) after 3 years of disease onset.

A similar study was made by Spanish neurologists (48). Clinical characteristics and the outcome of 7 patients (3 M, 4 F) with neurological involvement among 25 patients with BS who were admitted to a neurology centre between 1996 and 2009 were surveyed. Neurological disease was due to dural sinus thrombosis, aseptic meningitis, focal symptomatic epilepsy and parenchymal brainstem and/or cerebellum lesions. Median age at the diagnosis of neurological disease was 29.0 years while the median time from diagnosis of BS to development of neurological disease was 1.7 years. One patient with extensive brain stem and cerebellar involvement unresponsive to immunosuppressives died. The clinical

outcome in the remaining patients was good, although all had a relapsing remitting disease course. Neurological symptoms among the 18 patients who did not fill the neuro-Behçet criteria were mainly due to primary headaches or psychiatric diseases.

An interesting study on cognitive impairment in neuro-Behçet came from the Akman-Demir group (49). They studied cognitive and behavioural profiles of 20 BS patients (13 M/ 7 F) with parenchymal involvement. They also evaluated 20 (5 M/ 15 F) age, disease duration, education and disability status matched patients with multiple sclerosis (MS) as a diseased control group. Only ambulatory cases with relapsing remitting or secondary progressive course were included. Patients with primary progressive disease, mainly spinal cord involvement, severe physical and/or cognitive disability and severe visual loss along those who were illiterate were excluded. As a result, Neuro-Behçet patients showed a poorer performance on several measures of cognitive status than MS patients, suggesting a more severe "frontal"-executive dysfunction.

#### *Gastrointestinal involvement*

Jung *et al.* evaluated the 5-year clinical course of 130 patients (60 M/ 70 F) with intestinal involvement admitted to a single centre between 1986 and 2011 (50). The majority of the patients (n=97, 74.6%) had a remission or mild clinical activity at 5 years, while only 33 patients (25.4%) had multiple relapses or chronic symptoms. The first year of the clinical course influenced the clinical course of the whole follow-up. Patients in the severe clinical course group were younger, and had a higher acute phase response, higher disease activity and lower albumin level at diagnosis than patients in the mild clinical course group. Volcano-shaped ulcers were more likely to be common in the severe clinical course group, while oval and geographic-shaped ulcers were more common in the mild clinical course group. The frequency of atypical ulcers and ileo-cecal involvement was similar in both groups. As expected, the severe clinical course group required more intensive medical and surgical treatment than the mild

clinical course group. The same group analysed a larger cohort (n=291) to see the influence of age at diagnosis and sex on the clinical course (15). Authors divided the patients into two groups: younger than 40 years of age (n=154) and older than 40 years of age (n=132). Younger age at diagnosis was associated with a higher leukocyte count, C-reactive protein (CRP) level, and disease activity index for intestinal BD, and with a greater prevalence of volcano-shaped ulcers and a definite diagnostic subtype. Moreover, the cumulative probabilities of operation, admission, and corticosteroid use were significantly higher in the younger group. Male sex was associated with a higher CRP level and a greater prevalence of volcano-shaped ulcers. In intestinal BD, younger age at diagnosis is associated with a more severe clinical course and a poorer prognosis.

Lee *et al.* reviewed the medical records of 167 intestinal BD patients between March 1986 and April 2011 and developed a novel endoscopic severity model for intestinal BS (51). They compared the feasibility of the new model with the actual disease activity index for intestinal Behçet's disease (DAIBD). The endoscopic severity model was developed based on selected endoscopic variables such as ileocecal vs. non-ileocecal area, shallow vs. deep ulcers, geographic-shaped ulcers vs. volcano-shaped ulcers. A multivariate regression analysis revealed that the number of intestinal ulcers and volcano shaped ulcers were independent predictive factors for the DAIBD. However, the correlation between endoscopic severity and DAIBD was weak.

We have previously discussed how it was difficult to differentiate Crohn's disease from BS (36). Both diseases have similar clinical and histopathological features. Now a recent study supports this argument by indicating that levels of CRP and ESR and WBC counts could not be used to distinguish Crohn's disease from BS patients (52). Whereas these markers could be well used to differentiate Crohn's from intestinal lymphoma.

#### *Erythema nodosum like lesions in BS*

A Japanese group reviewed the clinico-

pathological features of erythema nodosum (EN)- like lesions in 26 patients (7 males, 19 females) with BS (53). The lesions were classified histopathologically into EN-type (septal panniculitis without vasculitis) and EN-like lesions of the vasculitis type. EN-type lesions were more likely to be seen among females with mild disease. On the other hand, EN-like lesions of the vasculitis type were associated with severe BS. These lesions were divided into the venulitis type and the phlebitis type, as previously observed (54). No arterioles or arteries were seen in these lesions.

#### *Renal involvement*

Cho *et al.* did a retrospective chart review to determine the prevalence and clinical significance of renal involvement in BS (55). Among the 2007 (584 M, 1423 F) BS patients registered between 2009 and 2011, haematuria was present in 412 (48 M, 364 F) (20.5%) and proteinuria in 29 (11M, 18 F)(1.4%) patients. Only 12 patients required renal biopsy. IgA nephropathy was the most common pathologic diagnosis followed by atherosclerosis, minor, crescentic and diabetic changes. Ten (83.3%) of the 12 BS patients had stable renal disease, 2 patients experienced disease progression of whom 1 died. None of the patients had amyloidosis.

#### *Ear nose and throat*

Cinar *et al.* studied the prevalence of hearing loss in 41 patients with BS and age and gender matched 41 healthy controls (56). Audiological examination revealed that the prevalence of sensorineural hearing loss was significantly higher in the BS (68%) than the control group (22%) ( $p<0.002$ ). Gurbuzler *et al.* on the other hand, investigated voice quality among 31 BS patients and healthy controls (57). They reported that BS impairs voice quality without visible laryngeal and hypopharyngeal involvement.

#### *Fibromyalgia*

Melikoglu and Melikoglu assessed the frequency of fibromyalgia in 100 (40 M, 60 F) BS patients (58). Eighteen (6 M, 12 F) of 100 BS patients were diagnosed as fibromyalgia. BS patients with

fibromyalgia were more likely to be female and more likely to complain from fatigue, headache, and arthralgia.

#### *Metabolic syndrome*

Yalcin *et al.* studied the frequency of metabolic syndrome among 86 patients with BS and 72 healthy controls (59). Metabolic syndrome was found to be significantly more common among BS (35.4%) patients compared to healthy controls (20%) ( $p=0.04$ ). The syndrome was more likely to be more common among women.

#### *Paediatric BS*

Al Mosawi *et al.* described demographic and clinical characteristics in 9 patients with juvenile onset BS (60). Median age at presentation was 7 years. Similar to what have been previously observed (61), authors reported an increased prevalence of familial aggregation (5/9) among the first degree relatives and a delay in the diagnosis ranging between 4 months and 6 years. There was one patient with Down syndrome. It was noted that neurological (4/9), gastrointestinal (5/9) and musculoskeletal manifestations (7/9) were somewhat more common in the current Iranian series compared to the previous juvenile series (60).

#### *Pregnancy*

Noel *et al.* studied the effect of pregnancy in a large series of BS patients (n=46) (62). In this retrospective study, a total of 76 pregnancies were analysed. The median disease duration before the pregnancy was 3 years. Thirty-seven pregnancies out of 76 (36%) were associated with flares, of which 18 occurred during the post-partum period. Flares were more likely to occur in patients with shorter disease duration (median: 2 vs. 6 years,  $p=0.0003$ ), suggesting that flares were associated with disease activity rather than pregnancy itself. The symptoms described during the flares were mostly oral (78%) and genital (68%) ulcers. It was noted that the annual incidence of flares/per patient was lower during the pregnancy as compared to that outside of pregnancy ( $0.49\pm 0.72$  vs.  $1.46\pm 2.42$  flares/year per patient,  $p=0.018$ ). Colchicine

(57%) and corticosteroids (22%) were the most common drugs used during the pregnancy. Apart from these, 4 patients received azathioprine, 1 was treated with thalidomide and another with cyclophosphamide. Twelve (16%) complications occurred in 9 patients which were mostly miscarriages. It was noted that patients with obstetrical complications were more likely to have past history of venous thrombosis.

#### Reviews

Apart from the clinical studies, various comprehensive reviews were published recently. These were an up to date review of the current literature by our group (63) and by Dalvi *et al.* (64), differential diagnosis (65) and imaging modalities of Behçet uveitis (66) by Ilknur Tugal Tutkun, current concept of paediatric onset BS (67) and neuro-Behçet's disease in childhood (68).

#### Management

With the exception of one randomised controlled trial of secukinumab, an anti-IL 17A antibody, last year's publication on the treatment of BS were predominated by uncontrolled case series and case reports on the efficacy and safety of biologic agents. It appears that TNF- $\alpha$  inhibitors become standard treatment for patients resistant to conventional immunosuppressives. Switching between biologics becomes a routine practice when the first or even second biologic agent is stopped for adverse events or inefficacy. Emerging treatments with novel biologics also appeared as case reports.

#### TNF- $\alpha$ inhibitors

Severe posterior uveitis that is refractory to conventional immunosuppressives is the main indication of TNF- $\alpha$  inhibitors in BS. Most of the experience for this indication comes from infliximab followed by adalimumab (69). The efficacy and safety of prolonged treatment with infliximab was the objective of a retrospective study consisting of 19 BS patients with severe uveitis (70). During a mean duration of 44 months, infliximab treatment resulted in a significant improvement of visual acuity, decrease in macular edema

and reduction of concomitant immunosuppressive medication. Infliximab could be withdrawn in 9 patients who remained in remission for a mean of 56 months. Four of these patients experienced disease flares between 3–10 months after withdrawal and again started infliximab. The remaining 5 patients maintained their complete remission during a mean follow-up of 25 months after withdrawal. The authors concluded that prolonged treatment with infliximab is safe and efficient in the management of refractory uveitis of BS and may result in sustained long-term remissions in a substantial portion of patients after withdrawal.

A retrospective study from Japan assessed the factors affecting the response to treatment with infliximab among 29 BS patients with uveitis (71). The patients were divided into 2 groups according to the presence (12 patients) or absence (17 patients) of ocular attacks under infliximab treatment for 12 months and their clinical characteristics were compared with data observed during 6 months prior to the initiation of infliximab. Treatment with infliximab was effective in decreasing the frequency of ocular attacks and in improving visual acuity in both groups. Patients with no attacks under infliximab therapy were younger at the onset of ocular inflammation, had a longer duration of ocular involvement and had less ocular attacks during the observation period before starting infliximab.

A prospective observational study evaluated the changes in health related quality of life (assessed with EuroQol-5D questionnaire) and vision related quality of life (assessed with National Eye Institute Visual Function Questionnaire) in 20 BS patients with uveitis receiving infliximab by comparing their scores before and under treatment (72). Treatment with infliximab significantly decreased the frequency of ocular attacks and overall disease activity and this was accompanied by significant improvements of the health related quality of life and vision related quality of life scores compared to pretreatment scores.

Gastrointestinal involvement is an important and difficult to treat complica-

tion of BS. A multicentre, retrospective study from Korea investigated the efficacy of infliximab in the treatment of intestinal involvement of BS (73). The study group consisted of 28 patients who were treated with infliximab 5 mg/kg for a median duration of 29.5 months (3–80 months) in 8 tertiary centres. Sixteen (57%) patients received scheduled infusions of infliximab at weeks 0, 2, and 6 and then every 8 weeks and the remaining 12 patients received episodic infusions of infliximab only on relapse of symptoms. Treatment with infliximab was found to be effective in achieving satisfactory clinical response and clinical remission rates during a follow-up of 54 weeks. Older age ( $\geq 40$  years) at diagnosis, female sex, a longer disease duration ( $\geq 5$  years), concomitant immunosuppressive use and achievement of remission at 4 weeks were found to be predictors of sustained response. The shape of intestinal ulcers, schedule of infliximab infusions, CRP normalisation after infliximab therapy and previous history of abdominal surgery had no impact in the response to infliximab therapy.

#### Switching between TNF- $\alpha$ inhibitors

A retrospective study assessed the efficacy and safety of switching to a second TNF- $\alpha$  inhibitor after failure to the first inhibitor (74). The study group consisted of 34 BS patients receiving TNF- $\alpha$  inhibitors (infliximab = 30 patients, adalimumab = 4 patients) for various indications in line with the EULAR recommendations. Nineteen of them switched to a second TNF- $\alpha$  inhibitor (etanercept = 6 patients, adalimumab = 12 patients and infliximab = 1 patient). The reasons were primary failure (no satisfactory response at 3 months) in 5 patients, early adverse events in 3 patients and secondary failure defined as having relapse after initial response in the remaining patients. Initial response rates were 76% (26 of 34 patients) to the first TNF- $\alpha$  inhibitor and 95% (18 of 19 patients) to the second TNF- $\alpha$  inhibitor. However, the duration of response was not long lasting with continuation rates at 24 months being 14% for the first TNF- $\alpha$  inhibitor and 22% for the second TNF- $\alpha$  inhibitor. The

safety profile of the second TNF- $\alpha$  inhibitor did not differ from that of the first TNF- $\alpha$  inhibitor.

#### Other biologics

Elevated levels of IL-17A have been found in the peripheral blood of patients with uveitis associated with diverse immune-mediated inflammatory diseases compared to healthy controls and patients with quiescent uveitis (75). The efficacy and safety of different doses of secukinumab, a fully human anti IL-17A monoclonal antibody, has been tested in 3 randomised, placebo-controlled and double-masked trials in 3 different patient populations (76). Enrolled patients were BS patients having posterior uveitis or panuveitis (SHIELD study), patients without BS having active, noninfectious uveitis (INSURE study) and patients without BS having quiescent, non-infectious uveitis (ENDURE study). Patients continued to their standard of-care systemic immunosuppressive therapy. In the 24-week SHIELD study, BS patients with active or quiescent uveitis who had experienced at least 2 exacerbations in the same eye (study eye) within the previous 6 months were randomly assigned to 3 treatment arms: Secukinumab 300 mg subcutaneously at baseline, week 1, and week 2 (loading phase) and then every 2 weeks; or secukinumab subcutaneously 300 mg at baseline and week 2 (loading dose) then monthly; or subcutaneous placebo at baseline, week 1, and week 2 (loading phase) then every 2 weeks. The SHIELD study enrolled 118 BS patients of whom 97 (82%) completed the study. The study failed to reach the primary outcome that was defined as reduction in the rate of recurrences in the study eye. The mean numbers of recurrences were 7.7 in the secukinumab every 2 weeks group, 11.5 in the secukinumab every 4 weeks group and 7.7 in the placebo group. On the other hand, the secondary outcome, defined as the tapering of immunosuppressive therapy in a step-wise fashion, was met in both groups. Adverse events, resulting in discontinuation of the study medication, were more frequent in both secukinumab groups. One patient in the secukinumab group

(300 mg every 4 weeks) died as a result of thromboembolic event but this was considered as being not related to study medication. The negative results of the SHIELD study led to early termination of the INSURE study by the sponsor. The ENDURE study was also terminated early when an interim analysis did not show any significant effects for any of the secukinumab groups compared to the placebo group. The high amount of concomitant immunosuppressive therapy in all treatment groups, the severe nature of the uveitis in study patients as well as the short duration of the trial could have also played a role in the negative results of these trials.

Two new case reports found tocilizumab (an IL-6 inhibitor) beneficial in refractory ocular and neurological involvement of BS (77, 78). In contrast, a negative result was reported for tocilizumab in 2 cases with severe mucocutaneous involvement (79). Further experience will help us to better understand whether these divergent results are by chance only or constitute further clues for the cluster hypothesis in BS claiming different pathogenetic mechanisms for different manifestations (80). Finally, 2 successful case reports with ustekinumab (an anti-p40 antibody) and alemtuzumab (anti CD52 antibody) suggest that the biologic armamentarium for BS will continue to grow in the future (81, 82).

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