Review

One year in review 2018: Behçet's syndrome

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Received on August 23, 2018; accepted in revised form on November 19, 2018.

Clin Exp Rheumatol 2018; 36 (Suppl. 115): S13-S27.

Key words: Behçet's syndrome, pathogenesis, outcome assessment, clinical findings, management

Competing interests: G. Hatemi has received research grant/research support and/or speaker fees from Abbvie, Celgene Corporation and UCB Pharma. E. Seyahi has received speaker fees from MSD, Novartis and UCB. V. Hamuryudan has received honoraria, speaker fees and research grants from Amgen, BMS, Johnson & Johnson, MSD, Novartis, Pfizer, Roche and UCB. The other authors have declared no competing interests.

ABSTRACT

New epidemiologic studies from Poland, Jordan, Algeria, Taiwan and Korea highlight the geographic differences in incidence, prevalence and clinical features of Behçet's syndrome (BS). A study from Austria comparing clinical manifestations of their BS patients with different countries of origin suggest that environmental factors may be important in the disease phenotype of BS. New genetic association studies dealing with the innate and acquired aspects of BS prevailed during 2017 and novel susceptibility and regulatory factors were described. Common denominators among various disease processes were again highlighted and epigenetic factors were emphasised. "Bagel sign" pattern, a central lesion with hypo-intense core and hyper-intense rim was defined in the spinal MRIs of the patients with neuro-BS especially during the acute attacks of myelopathy. This distinctive pattern suggests venous thrombosis and surrounding oedema in the spinal cord. Pseudotumour cerebri may present with similar clinical presentation to that observed in cerebral venous sinus thrombosis, responds well to immunosuppressive treatment, and could be associated with venous thrombotic relapses. Menstruation and certain food appear to exacerbate skin and mucosa lesions in BS. The EULAR recommendations for the treatment of BS have been updated with 5 new overarching principles and one additional recommendation for surgical management of vascular complications. Infliximab initiated earlier in the course of uveitis yields a better visual outcome. Tapering or stopping of anti-TNF agents seem to be possible when remission has been achieved. Adalimumab appears to be more effective for venous thrombosis than classical immunosuppressives. Oral anticoagulants might not be crucial for cerebral or peripheral venous thrombosis. Transcatheter embolisation of pulmonary aneurysms may be life-saving by providing immediate control of haemoptysis. The results of surgery for pulmonary artery involvement appear to be satisfactory.

Introduction

Behçet's syndrome (BS) is a variable vessel vasculitis that follows a relapsing and remitting course. The heterogeneity in clinical manifestations that can include oral and genital ulcers, nodular and papulopustular lesions, peripheral arthritis, uveitis, arterial aneurysms, venous and arterial thrombosis, central nervous system involvement and intestinal ulcers, can cause challenges in the diagnosis, management and disease assessment of BS. Several interesting studies have been published during the last 12 months regarding the epidemiology, pathogenesis, clinical findings and management of BS. As we had done in the previously published annual reviews, we have tried to provide a critical review of these recent studies (1-6).

Epidemiology

Studies describing and comparing the prevalance and disease characteristics of a condition among immigrants and natives of a geographic region are interesting, since they may point out the role of genetic and environmental factors in the development of that condition. A recent study from Austria reports on the disease manifestations of 76 patients with BS (7). Among these, 39.1% were of Austrian origin, 37.0% of Turkish origin and the remaining patients were of Italian, Balkanese, German, Armenian, Portuguese, Thai and Tunisian origin. The authors observed that the clinical findings of their patients with Turkish origin were similar to their patients with Austrian origin

and not to the previously reported clinical findings of Turkish patients living in Turkey, supporting a more pronounced role of environmental factors. Main differences were fewer genital ulcers and skin lesions and more frequent vascular, neurologic and gastrointestinal involvement in Turkish origin patients living in Austria. In a previous study from Germany, the disease manifestations were similar among BS patients of German and Turkish origin, whereas eye involvement was more frequent among patients of Turkish origin living in Turkey compared to a historic cohort of Turkish BS patients living in Turkey (8). On the other hand, a study from France had showed higher neurologic involvement and mortality rates among patients of North African origin compared to patients of French origin, all living in France (9). An important information missing from all of these studies that could help to speculate on the role of environmental factors in disease expression, is whether the immigrants are first, second or later generation immigrants and the age at immigration for first generation immigrants.

The first prevalence studies of BS in Poland (10) and in Jordan (11) were published last year, as well as the first epidemiologic study on BS in Algeria (12). The Polish study was also the first BS prevalence study from Eastern Europe and showed an incidence rate of 0.5 per 1,000,000 per year (95% CI 0.35–0.61) and a point prevalence of 0.34 per 100,000. This is to our knowledge the lowest prevalence rate reported in Europe after Scotland. In addition to a real difference in prevalence related to genetic and environmental factors, a lower immigration rate from BS prevalent countries and methodologic differences may be responsible for this low prevalence (13). This was a hospital-based study and only patients who were hospitalised as inpatients were captured. The authors suggest that systemic vasculitides with multi-organ involvement such as BS are usually hospitalised in Poland, but this may have caused some under-reporting since milder patients with only skin and mucosa involvement may be missing. The older age at diagnosis (41.6 years, 95% CI, 38.3-44.8) may point out to a delay in diagnosis, or may be related to the study design, since more serious complications of BS such as arterial, nervous system and gastrointestinal system involvement that would require hospitalisation, usually occur at a later age. Interestingly, no difference in prevalence was observed between urban and rural regions of Poland and 58.5% of BS patients were women.

The study from Jordan was conducted among 2469 hospital employees at 6 hospitals in North Jordan (11). Patients with recurrent oral ulcers, a previous diagnosis of BS or any major symptom suggesting BS were questioned and examined by 2 rheumatologists and a pathergy test was performed. A total of 17 patients who fulfilled the International Study Group (ISG) criteria were identified and 10 of these already had a previous diagnosis of BS. Mean age was 38.6±10.7 years and male to female ratio was 2.4:1. The estimated prevalence was 660 per 100,000 (95% CI 348–975), and this is the highest BS prevalence reported until now. A previous BS prevalence study among hospital employees in Turkey had shown an estimated prevalence of 440 per 100,000 (95% CI 220–780) (14). This result was similar to the estimated prevalence reported in a population-based study in the same city and authors had commented that studying hospital employees with comparable social/economic status may be a relatively simple, cheap and feasible method for estimating disease prevalence. In the study from Jordan, a family history of BS was reported by 25% of BS patients compared to 2.6% of hospital employees who did not have BS. It is not clear whether some of the index cases were from the same family, as this would also explain the high BS prevalence and the high family history rate.

The report from Algeria is a retrospective observational study describing the epidemiologic and clinical features of all BS patients followed in a University hospital in Algeria between 1990 and 2015 (12). A total of 61 patients were included with a male to female ratio of 4.1:1. The mean age at disease onset was 27.2±7 years and the time between onset of symptoms and diagnosis of BS was 4.8±6.3 years. HLA B51 was tested in 6 of the patients and was positive in only 1 patient (16.6%). Pathergy test was positive in 20% of the patients. All patients had oral ulcers whereas 60% had genital ulcers, 13.5% had nodular lesions, 56.4% had papulopustular lesions and 50% had arthritis. Uveitis was observed in 71.2% of the patients. Among these, 50% had anterior uveitis, 34.5% had intermediate uveitis, 38.7% had posterior uveitis, and 37.5% had panuveitis. Similar to other reports from the Mediterranean, vascular involvement was quite frequent. It was mostly in the form of venous involvement and was observed in 29.6% of the patients. Deep vein thrombosis was observed in 17.6%, superficial thrombophlebitis in 12.5%, subclavian vein thrombosis in 4.5%, cerebral venous thrombosis in 5.9% and intracardiac and vena cava inferior thrombosis in 3.9%. Arterial involvement was observed in only 2 patients. Additionally, 19% of the patients had central nervous system and 7.5% had gastrointestinal involvement.

Another epidemiologic study came from Taiwan, reporting on the incidence of BS in Taiwan using the nationwide reimbursement database including all ambulatory and inpatient records (15). The average incidence density between 2001 and 2011 was estimated as 2.40 cases per 100,000 person-years (range 1.29–3.53). This is higher than the incidence rate between 2005 and 2009 in Taiwan, reported as 0.9 per 100,000 person-years (95% CI 0.6–1.1) by another group, again using the nationwide reimbursement database (16). Interestingly, a diagnosis of BS was made more often among people aged 40 to 65 years compared to those between 18 to 40 years (cumulative incidence 37.1 cases per 100,000 person-years and 27.8 cases per 100,000 person-years, respectively). The authors point out the possibility of over-estimating the risk among patients between the ages of 40 to 65, if there were patients with a previous diagnosis of BS who were in remission for a long time before experiencing a recurrence after the age of 40

and thus were misclassifed as incident cases. BS was more frequent among women with a male to female ratio of 2:3. 67% of the patients were from urban areas, 28% from suburban areas and 5% from rural areas. Uveitis was diagnosed in 18.2% of the patients. Although more immunomodulators had been prescribed to patients with uveitis, the overall health-care expenditure was similar between patients with and without uveitis.

A nationwide population-based cohort study that explored the incidence of BS in Korea between 2006 and 2015 was conducted using the Korean National Health Insurance Claims Database (17). The annual incidence was estimated as 3.98 per 100,000 person-years. BS was more common among women with an incidence of 5.37 among women and 2.59 among men per 100,000 person-years. The highest incidence according to age was observed among people in their forties (6.56 per 100,000 person-year). The authors reported a significantly higher incidence of BS in subjects with comorbid metabolic conditions, such as diabetes mellitus, hypertension and dyslipidaemia. The mean prevalence was reported as 26.195±0.424 patients per 100,000 individuals from 2006 to 2015. A study from Korea that was published last year, using the Healthcare Bigdata Hub of the Health Insurance Review & Assessment Service had reported the prevalence of BS from 2011 to 2015 as gradually increasing and ranging from 32.8 to 35.7 per 100,000 population over the study period (18). Authors did not mention the previous study or comment on the possible reasons for this difference such as the use of different data sources or inclusion of data from 2006 to 2015 in the study by Lee *et al*.

Pathogenesis

Vascular endothelial growth factor (VEGF) still continues to have a putative role in the pathogenesis of BS. Recently, a study that aimed at comparing vascular endothelial growth factor (VEGF) and soluble vascular endothelial growth factor receptor-1 (sVEGFR-1) levels in BS was published (19). It evaluated BS patients having or not having serious organ involvement, disease activation and especially vascular involvement. Fifty-five patients with BS, 25 of which had vascular involvement, and 31 control subjects were included in the study. The serum VEGF and sVEGFR-1 levels in patients with BS were significantly higher than that in controls while difference in VEGF/sVEGFR-1 ratio was obtained close to borderline of significance. The study results suggested that elevated serum VEGF, sVEGFR-1, and more importantly VEGF/sVEGFR-1 ratio could play an important role in the development of thrombosis in BS (19). The reason(s) for the thrombotic tendency in BS is not well known. Vascular injury, loss and dysfunction/hyperfunction of endothelial cells are believed to play a role in thrombosis development. Injury and inflammation due to vasculitis can cause platelet response with increase in mean platelet volume (MPV) and thrombosis in BS. A recent study from Ankara compared the levels of MPV between patients with BS and healthy controls, and aimed to assess its effects on thrombosis (20). One hundred patients with BS and 100 age and gender matched healthy controls were evaluated for MPV levels with clinical findings in a case-control study. Mean MPV was significantly higher in patients with BS than healthy controls. Platelet counts were lower than controls, but not significantly. In addition, a negative correlation was found between platelet count and MPV in patients and the presence of erythema nodosum (EN) and MPV were determined as predictors for vascular involvement and thrombosis. The study suggested that MPV is a simple measurement for indirect monitoring of platelet activity and thrombotic potential (20). Another interesting paper investigated whether there is a difference between male and female patients with BS in terms of hypercoagulability by using modified rotational thromboelastograhic (ROTEM) analysis; 126 BS patients were included in the study (21). Moreover, 23 patients with vasculitis, and 25 healthy individuals were included as disease and healthy control (HC) groups, respectively. Clotting time (CT), clot formation time (CFT) and maximum clot firmness (MCF) were determined by INTEM and EXTEM analyses. As a marker of vascular endothelial injury, along with inflammatory markers, vWFag levels were investigated in patients and HC group. The results showed that Extem-CFT was shorter in only vasculitic group compared to HC group. Intem-CFT was found to be shorter in BS patients and vasculitis group compared to HC and Intem-MCF was significantly longer in male BS patients than female BS patients. In addition, Extem-CFT was found to be shorter in male BS patients compared to female BS patients. These results support that male BS patients have a hypercoagulable state compared to female BS patients, which may explain why male patients are prone to thrombotic complications (21).

Regarding the potential diagnostic value of serological biomarkers, a recent study adopted a proteomic strategy for immune complexome in order to screen novel autoantigens or autoantibodies in circulating immune complexes (CICs) from BS patients (22). CICs were separated from serum sample of 10 BS patients and 10 healthy controls and then subjected to Orbitrap mass spectrometry for autoantigen profiling. The results of the study showed that a total of 17 potential antigens were identified in CICs from BS patients, but not in HC. The autoantibody to one of the identified antigens, tubulin-α-1c, was significantly increased in BS patients compared with that in healthy and disease controls. The sensitivity and specificity of tubulin-α-1c antibody in the diagnosis of BS in this study were 61.36% and 88.4%, respectively. Further analysis demonstrated that anti-tubulin-α-1c was associated with complications of deep venous thrombosis and erythema nodosum in BD. Therefore, anti-tubulin-α-1c antibody seems to be a promising biomarker in diagnosis and severity evaluation of BS, indicating the risk of deep venous thrombosis and erythema nodosum (22). Another study aimed at evaluating the diagnostic potential of antibodies to zymogen granule glycoprotein GP2 (aGP2) in a large, well-defined Chinese cohort

with a special focus on their role in discriminating CD from intestinal BS and intestinal tuberculosis (ITB) (23). A total of 577 subjects were prospectively enrolled, including 171 patients with CD, 208 patients with ulcerative colitis (UC), 71 with BS, 57 with ITB and 70 healthy controls (HC). aGP2 and anti-Saccharomyces cerevisiae antibodies (ASCA) were determined by ELISA. Notably, aGP2 IgG and IgA levels were significantly elevated in patients with CD compared with those in patients with UC, intestinal BS, ITB and HC. Conversely, ASCA IgG levels were not different between CD and intestinal BS patients, whereas ASCA IgA levels did not discriminate CD from intestinal BS and ITB patients. Moreover, ASCA IgA did not discriminate CD from disease controls; aGP2 IgA and/or IgG was significantly associated with penetrating disease (B3) and ileal CD (L1) ($p<0.05$), whereas ASCA IgA and/or IgG was not. Therefore, in comparison with ASCA, aGP2 distinguishes CD from intestinal BD or ITB as disease controls more efficiently, aiding in the differential diagnosis of IBD (23).

An apparently unprovoked recurrent inflammation is the quintessential hallmark of autoinflammatory diseases and, in this regard, growing data exist regarding the use of nutrition supplements in their management (24). Among these, curcumin is considered to be a bio-active agent since it has anti-inflammatory properties. Recently, a study investigated the effect of curcumin on the inflammatory cytokines expression and production in M1 macrophages from BS patients compared with healthy controls. Monocytes were collected from 10 healthy controls and 20 active BS patients, differentiated to macrophages by macrophage-colony stimulating factor for 7 days. Macrophages were then treated with interferon gamma, lipopolysaccharide, and curcumin (10 or 30 μg/ml) for 24 h. Treatment with 30 μg/ml curcumin significantly down-regulated mRNA expression of IL-1β ($p<0.05$) and protein production of IL-6 ($p<0.05$) in M1 macrophages from BS patients but not in M1 macrophages from controls; moreover it seems to significantly diminish the protein production of TNF-α in M1 macrophages of BS patients ($p<0.01$) and healthy controls ($p<0.05$) (25).

Other interesting data come from studies that investigated the putative diagnostic role of antigens and antibodies in BS. A recent study assessed IgM anti-alpha-enolase antibodies (AAEA) in BS and its possible association with clinical manifestations and disease activity (26). Ninety-seven consecutively selected BS patients were compared to 36 patients with enteropathic spondyloarthritis (ESpA) [24 Crohn's disease (CD) and 12 ulcerative colitis (UC)] patients and 87 healthy controls. IgM AAEA was detected by immunoblotting. Disease activity was assessed by standardised indexes. A second evaluation was performed in BS patients (n=56), regarding IgM AAEA presence, disease activity scores and C-reactive protein (CRP) levels. The authors found higher IgM AAEA frequency in BS patients (17.7%) compared to EspA (2.8%) and healthy controls (2.3%), $p<0.001$. IgM AAEA frequency was higher in active BS compared to inactive BS patients (30.2% *vs*. 7.4%, $p=0.006$), a finding confirmed in the second cross-sectional evaluation of 56 of these BD patients (45.5% *vs*. 13.3%, $p=0.02$). These data support the long held idea (27, 28) that alpha-enolase is a target antigen in BS, particularly associated with disease activity, mucocutaneous and articular involvement. In addition, IgM AAEA may distinguish BD from ESpA, especially in patients with high disease activity (26). Another possible pathogenetic mechanism in BS is represented by anti-endothelial cell antibodies (AECA); one of the endothelial cell antibodies was reported to recognise alpha-enolase. This aspect has been re-evaluated by a recent study that was aimed at investigating the expression of alpha-enolase in the surface of peripheral blood cells and serum anti-alpha-enolase antibody (AEA), and their association with clinical manifestations or disease activity of BS (27). The frequency of surface alpha-enolase-expressing cells was increased in BS in lymphocytes and monocytes and serum AEA levels were increased in BS patients, particularly with mucocutaneous involvement compared to HC. Moreover, the levels of AEA were correlated with the number of oral ulcers, erythrocyte sedimentation rate and CRP levels (29).

Another study investigated CXC chemokines and its receptor in patients with BS and their associations with disease activity (30). Blood samples were collected from 109 BS patients and 36 age- and sex-matched HC. Twenty-two follow-up blood samples were collected in BS patients. Serum CXC chemokines (CXCL1, CXCL8, CXCL9, CXCL10, CXCL12, CXCL13 and CXCL16) and cell surface marker expression (CD3, CD4 and CXCR3) in peripheral blood mononuclear cells (PBMCs) were assayed. In follow-up BS patients, changes in serum CXCL10 levels tended to be correlated with changes in Behçet's disease current activity index scores. The percentage of CXCR3 expression in CD3-positive cells in PBMCs was inversely correlated with serum CXCL10 levels in BS patients. By immunohistochemistry, the number of CXCR3-positive mononuclear cells was higher in skin and intestinal lesions of BD patients than in those of HC. These results suggest that the CXCL10/CXCR3 axis may contribute to the pathogenesis of BD (30).

Soluble CD40 ligand (sCD40L) represents another important mediator of inflammation in BS. A recent study tried to investigate the role of plasma and the CD40L pathway on NET release and the oxidative burst profile in patients with active and inactive BS (31). Neutrophils and peripheral blood mononuclear cells (PBMCs) were obtained from patients with active BS (n=30), patients with inactive BS (n=31), and HC (n=30). sCD40L plasma levels were significantly higher in patients with inactive BS and patients with active BS than in HC and NET release was constitutively increased in BS compared with HC. Moreover, NET release and H2O2/O2- were higher after stimulation with sCD40L or BS plasma and decreased after sCD40L blockade. Globally, the results showed that plasma from patients with active BS

exerts a stimulus on NET release and oxidative burst, probably induced by sCD40L (31).

Several studies investigated the role of cytokines in the pathogenesis of BS. Among these, a study investigated TSLP and IL-33 in BS and tried to prove the effect of the anti-inflammatory cytokine IL-37 in BS skin lesions on TSLP production (32). TSLP, IL-33 and GATA-3/T-bet, were measured using PCR in BS skin lesions. The authors tested the suppressive effect of IL-37 on skin samples stimulated with a cytokine mixture inducing TSLP expression. TSLP and IL-33 were increased in BS patients particularly in patients having skin manifestations and correlated with indexed skin lesions (32). Another study tried to find out possible differences at early stages in the transcription factors/cytokines expression profiles in blood and cerebrospinal fluid (CSF) of Multiple Sclerosis (MS) and BS patients with nervous system involvement, which could be useful discriminative markers (33). The most striking finding was the significant increase of CSF IL-10 that the authors observed only in BS patients with nervous system involvement. The authors suggested that CSF IL-10 level may be a predictive marker to help clinicians discriminate between these two neurological disorders (33). Results from another study indicated that IL-17 A/F, IL-23 and IL-12/23 (p40) may play role in the immunopathogenesis of BS (34). Since Th17 and Th1 cell responses and since IL-35 levels seem to be lower in active BS patients compared to inactive patients and HC, there may be a plasticity between Th17 and Treg cells according to the state of disease activity (34).

It has been suggested higher serum levels of IL-15 and lower expression levels of IL-15 receptor alpha (IL-15Rα) are correlated with pathogenesis of BS. However, whether overexpressing IL-15Rα could be used as a therapeutic candidate for BS is currently unclear. A recent study aimed at evaluating whether overexpressing IL-15Rα could affect BS symptoms in a mouse model (35). IL-15/IL-15Rα complex expressing vector or protein complex of IL-15/IL-15Rα-Fc was used to treat BS mice. The results of the study suggested that up-regulating IL-15Rα+ cells could be used as novel therapeutic strategies to control BS in the future (35). Another interesting study explored IL-26 levels in serum, bronchoalveolar lavage fluid (BAL) and cerebrospinal fluid (CSF) from active BS patients (36). Samples were collected from 95 BS patients (55 patients were in active stage) and 50 HC. They were investigated with ELISA for estimation of cytokines levels. Serum concentration of IL-26 resulted higher in both active [4.80±1.32] and inactive [2.77±1.026] BS compared to HC [0.31±0.14ng/ml; $p<0.0001$]. In addition, level of IL-26 was associated with the BS clinical severity score from moderate to severe and IL-26 was highly expressed in CSF [10.80±2.05ng/ml] and in bronchoalveolar lavage fluid [12.89±3.03ng/ml] from BS patients compared to their respective controls. IL-26 levels in CSF and in bronchoalveolar lavage fluid showed positive correlations with IL-17 level and an inversely correlation with IL-37. Interestingly, IL-26-stimulated $CD4^+$ T cells and monocytes promote the generation of Th17 (IL-17A, IL-23) and suppress Treg (IL-10, TGF-β) cytokines. The results may suggest a signature of IL-26 probably responsible for the inflammatory process to correlate positively with Th17 cytokines and inversely with Treg mediators (36).

Genetics

A Korean group intended to fine map the loci of IL23R-IL12RB2, IL-10, STAT 4 and ERAP1 for BS disease associations, given the fact that they were previously related to disease susceptibility in the Japanese, Turkish and Chinese populations (37). They used the imputation technique with the aim of enhancing SNP density and utilised 369 BS patients and 2000 controls in the discovery group and 84 *vs*. 283 in the replication group. Only the IL23R-IL12RB2 loci had a significant association with BS whereas the remaining three did not. Furthermore, they were mapped on the intergenic region rather than the two flanking genes (37).

Another study tested the frequency of SNP's in the IL23R-IL12RB2 and IL-10 regions in 89 Israeli and Turkish BS patients with uveitis. The A allele in rs1800871 of the IL-10 gene was highly prevalent in BS and healthy control samples alike and were especially high among the Turkish patients. The G allele in rs1495965 in the IL23R-IL12RB2 gene was high in BS uveitis and among healthy Turkish and Israelis of Middle Eastern origin while lower among the other Israeli control group (77.9%, 78.9%, 27.8% respectively, $p<0.001$) highlighting the differences between the populations. The main limitation of this study was the small study group and the limited number of tested SNP's (38). A Chinese group studied the association between TNFSF4, TNFSF8 and TNFSF15 in 796 patients with BS, 792 with Vogt Koyanagi Harada (VKH) and 1604 healthy controls, taking into account the observation that the tumour necrosis factor superfamily (TNFSF) and its respective receptor superfamily (TNFRSF) play critical roles in immune homeostasis, cell death and inflammation (39). Thirty-five SNP's were selected based on earlier disease association studies. The A allele and AA genotype frequencies of TNFSF4/rs1234313 were significantly increased and the GG genotype frequency of rs123431 was decreased in subjects with BS. Significantly lower frequencies of the C allele and the CC genotype and higher frequency of the TT and CT genotypes of TNFSF15/rs4246905 were observed in BS patients. Moreover the frequency of the A allele of TNFSF8/rs7028891 was also lower in BS. These changes were not prominent in the VKH and the controls suggesting that they may be important in BS disease pathogenesis (39).

Previous studies had shown that vitamin D had an immunomodulatory function through inhibition of T cell activation, B cell immunoglobulin production and secretion of various cytokines. The controversial findings of serum vitamin D levels in BS has prompted a meta-analysis of vitamin D receptor polymorphisms and susceptibility to this condition (40). A total of six seperate comparisons of 468 cases and 516 controls were included.

It was demonstrated that the A allele of ApaI and F allele of FokI polymorphisms were associated with BS in the total and especially the African populations whereas ApaI was predominant in Caucasians. No relationship was determined between BsmI and TaqI polymorphisms and disease risk (40).

A review article commented on the controversial issue of BS as a "MHC-I-opathy" initially proposed my McGonagle *et al*. (41). It proposed that altered peptide presentation by HLA-B51 is vital to the disease process and suggested that especially natural killer or other cell interactions mediated by leukocyte immunoglobulin-like receptor (LILR) or killer immunoglobulin-like receptors (KIR) are crucial in this process of presentation (42). They also pondered on the possible direct effect of HLA misfolding on the inflammation of BS (42).

The role of the defects of the natural killer (NK) cell repertoire in BS and their relationship with KIR receptors and HLA genes was investigated in an Iranian study performed on 397 BS patients and 300 healthy controls (43). None of the KIR genes showed significant effects on BS susceptibility. HLA-C1 Asn80 showed a protective effect against BS whereas HLA-C2Lys80, HLA-B-Bw4Ile80, HLA-B5 and HLA-B51 were associated with a susceptibility risk for BS. Concerning the combination of KIR and HLA genes, HLA genotypes no 2,3,5 and 8 and inhibitory KIR no 4 were significantly higher in patients than controls whereas KIR genotype 3 HLA genotypes 1, 4, 6, 7 and 9 were significantly lower. These suggested that the KIR-HLA repertoire is important in disease pathogenesis (43).

Taking into account the possible contribution of autoinflammation in the pathogenesis of BS, a Spanish group investigated the role of rare variants of seven inflammasome related genes: CECR1, MEVF, MVK, NLRP3, NOD2, PSTPIP1 and TNFRSF1A (44). They used a next generation sequencing approach among 355 BS patients. The results supported the influence of variants of NOD, PSTPIP1 and MVK with NOD2 as the major contributors. They also suggested that some variants may play a role in the inflammatory process whereas others may be polymorphisms that do not have a concrete significance (44).

C-type lectin receptors (CLR) are a large group of extracellular proteins expressed on immune cells that act as pattern recognition receptors. They play an important role in anti-inflammatory immune responses as well as in the maintenance of host-immune homeostasis. Various members of CLR are associated with immune mediated diseases and a Chinese study has concentrated on gene polymorphisms of CLR in BS patients (45). 766 patients and 1674 healthy controls were recruited from a Chinese Han population and various mannose binding lectin (MBL2) and killer cell lectin like receptor (KLRC4) polymorphisms were studied. MBL2/rs1800450 and KLRC4/rs2617170 were susceptibility factors for BS (45).

A Turkish group investigated the role of P-selectin glycoprotein ligand -1 (PSGL-1) variable number of tandem repeat (VNTR) polymorphism on the risk of thrombosis in BS, a risk factor of increased thrombosis in the antiphospholipid syndrome (46). They studied 136 BS patients with thrombosis (112 male, 24 female), 120 BS patients without thrombosis (54 male, 66 female) and 190 healthy controls (103 male and 87 female). They did not find a significant relationship between the polymorphism and the tendency to thrombosis (46).

A study was performed among 1238 BS patients with uveitis and 1458 healthy controls in a Chinese Han population with the aim of delineating new genetic associations that had emerged in recent studies (47). Four SNP's were associated with BS and it was postulated that LACC1, CEBPB-PTPN1, ADO-EGR2 and RIPK2, genes implicated in the shared pathogenetic pathways with other diseases such as leprosy, were also implicated in this condition (47).

Fc receptors have an important role in the initiation and regulation of many inflammatory processes and a study in a Chinese Han population investigated Fc receptor family gene polymorphisms in 1022 BS patients with ocular manifestations and 1803 healthy controls (48). A significantly higher frequency of the FCGR3A/rs428888 CT genotype (OR:1.897) and a lower frequency of CC genotype and C allele (OR: 0.554) were found in ocular BS compared to controls. Functional experiments showed an increased expression of FCGR3A and increased cytokine prtoein expressions of MCP-1, IL-1beta and TNF-alpha in CT carriers of FCGR3A rs428888 compared to CC carriers (48). This study deserves merit for including a well-defined subset of BS patients, those with uveitis, in contrast to many other genetic studies that lump together BS patients with different phenotypes, forming a heterogenous group.

Another study from China conducted in 906 patients with ocular BS and 2178 healthy controls, investigated the association of genetic variations in PTPN2 and CD122, the tyrosine phosphatases that are implicated in various autoimmune diseases (49). The results revealed that the AG phenotype of PTPN2 rs7234029 conferred a disease risk for BS, whereas the GG genotype of this locus had a protective effect on BS. Functional studies showed that the GG genotype of rs7234029 carriers had a higher PNPT2 mRNA expression level than those carrying the AA or AG genotype. Additionally these findings were strongly influenced by gender and were more prominent in males (49).

A Chinese Netherlands collaborative study investigated the role of long non-coding RNAs polymorphisms, a group of non-coding potential transcripts implicated in various biological processes and in the development of autoimmunity (50). They genotyped 110 SNP's in 1626 patients with VKH, 384 BS, 624 anterior uveitis with AS, 751 anterior uveitis without AS, 720 AS without anterior uveitis and 3305 healthy subjects. No significant association was determined in BS patients (50).

Another Chinese Netherlands collaborative study investigated the DNA methylation patterns of transcriptional and inflammatory factors in 16 BS and 18 healthy controls (51). They found that the promoter methylation level of GATA3, IL-4 and TGF-beta was sig-

nificantly up-regulated in active BS patients and negatively correlated with the corresponding mRNA expression. Their results suggested an aberrant DNA methylation that has the potential to result in gene transcriptional silencing (51).

A study from Turkey conducted in a small number of patients and controls (40 BS and 30 healthy individuals) found higher gene expression levels of IL18, IFNG, IFNGR and CRP in a subgroup with active uveitis compared to controls and no significant differences in IL10 and HSP 70 levels between the two groups (52).

IRAKs (IL-1 receptor associated kinases) are key components in the signal transduction pathways utilised by IL-1R, interleukin-18 receptor and toll like receptors. The expression and function of IRAK1 and 4 were investigated among 28 BS patients and 32 normal subjects (53). The mRNA levels of IRAK 1 and 4 were both significantly increased in active BS patients compared with inactive BS and normal controls suggesting that these receptor kinases might participate in disease pathogenesis (53).

A Korean group evaluated thiopurine S-methyltransferase polymorphisms, an enzyme that affects the metabolism of thiopurine drugs with the potential of causing toxicity, among 149 patients (116 BS) in a dermatological setting (54). The most common mutant allele was TPMT*3C with a frequency of 3.4% consistent with the Korean data for other inflammatory diseases. One TPMT*6 allele was also detected in a patient with BS. Complications with azathioprine were related only to the wild type allele and there were no serious side effects related to azathioprine among the patients with the mutations (54).

A study among 111 patients with BS and 100 healthy controls investigated the possible association of the macrophage migration inhibitory factor (MIF)-173 GC variant in this condition (49). The homo genotype CC was more prevalent in the patient group compared to controls (OR: 0.24 CI: 0.05-0.78) suggesting that it may be a risk factor for BS (55).

Another study evaluated interleukin-1 receptor antagonist (IL-1RA) gene 86 bp variable number tandem repeat (VNTR) variant among 109 Turkish patients with BS and 100 healthy controls (56). The genotype distribution and the allele frequencies of the IL-1Ra VNTR variant did not differ between the patients and the controls (56).

Franco-Jarava *et al*. from Spain described a patient who had fevers, neutrophilic dermatosis, recurrent oral and genital ulcers and who had a 13.13 Mb deletion on chromosome 6 including the TNFAIP3 gene (A20), a potent inhibitor of the NF-kappaB signalling pathway (57). This was presented as a possible mechanism of autoinflammation having implications for BS although the patient lacked the specific features of the condition (57).

Investigators from Italy used a gene array strategy to identify transcriptional profiles of peripheral blood cells obtained from 51 patients with BS (58). Th17 and type 1 interferon inducible genes were found to be upregulated and the Th17 polarisation was confirmed. There were 5 clusters enriched in T and B cell activation pathways and 2 clusters enriched in type 1 IFN, JAK/STAT and TLR pathways. Given that all of these are important in autoimmunity, the authors claimed that an autoimmune pathology was also operative in BS (58). A microarray profile performed by the same group identified specific miRNA signatures associated with active BS. These targeted the TNF, IFN gamma, and VEGF-VEGFR signalling cascades (59).

A recently published review article summarised the immunopathogenesis of BS with detailed descriptions of the HLA-B51 association, increased neutrophil motility and superoxide production, elevated quantities of TNF-alpha and IL-10, the Th17 polarisation and the genetic and epigenetic findings and discussed novel treatment strategies (60).

Clinical manifestations

A study run by the Japanese Ministry of Health, analysed a nationwide inception cohort of 7950 patients registered between 2003-2014, aiming to find the frequency of those who do and do not fulfil the Japanese criteria and also those who fit the definition of 'variant cases' (61). Patients were categorised into either of the complete type, incomplete type, and possible case according to these criteria. For those who are not satisfying complete/incomplete criteria but have either of the intestinal, vascular, or neurological involvement are called as 'variant types'. Researchers paid particular interest to those who had possible variant cases. The study found that 6344 (79.8%) fulfilled the Japanese criteria (complete type: 11.0%, incomplete type: 59.4%, possible: 9.4%), while the remaining 1606 (20.2%) were defined as variant types (complete type: 0.8%, incomplete type: 10.7% and possible: 8.7%). Among the 694 patients who had variant-type possible BS, 479 had entero-, 46 vasculo-, and 169 neuro-variant possible BS. The study also revealed that the entero-variant possible cases were less likely to have eye involvement, whereas those with vasculo-variant cases were less likely to have genital ulceration and more likely to carry HLA-B51. On the other hand neuro-variant cases were more likely to be older at diagnosis.

Eye disease

Similar to what has been shown in a previous epidemiological survey from Turkey (62), BS was found to be the most common identifiable cause of inflammatory uveitis as shown in a study with a rather small sample size (n=235) conducted in a university hospital between 2013 and 2014 in Iran (63). Idiopathic uveitis was the most common cause (28.5%), followed by Behçet's uveitis (16.6%), Vogt-Kayanagi-Harada (10.6%), Herpes (8.9%) and spondylarthropathies (6.8%). A study using the nationwide Japanese registration database investigated the association of eye lesions with demographic findings and extraocular manifestations among BS patients particularly in the early phase of the disease (64). Among 3213 patients with confirmed or possible BS, those with ocular disease were less likely to be female, and were less likely to have genital ulceration and gastrointestinal involvement. A retrospective survey from Cairo Univer-

sity investigated demographic factors associated with severe ocular disease in 249 BS patients followed between 2012 and 2017 (65). In line with the Japanese registry data, they observed that patients with more severe ocular disease were less likely to have genital ulcers and vascular involvement. Both studies, support phenotypical clustering in BS.

Optical coherence tomography (OCT), which emerges as an alternative non-invasive method in monitoring macular ischaemia, was again popular this year: 3 studies evaluated its role in Behçet's uveitis (66-68). First study analysed choroid morphology using OCT during attacks in 28 patients and 28 controls (66). Choroidal stroma-to-choroidal vessel lumen ratio was significantly higher in patients, whereas there were no significant differences in subfoveal choroidal thickness between patients and controls. Choroidal stroma-to choroidal vessel lumen ratio correlated with retinal vascular staining and leakage score in fluorescein angiography. Central foveal thickness was significantly increased in patients and showed significant correlations with clinical and angiographic ocular activity scores. Diagnostic sensitivity and specificity of central foveal thickness for acute Behçet's uveitis were 89% and 72%, respectively. Second study evaluated the choroidal thickness during 3 different clinical stages defined as acute, remission, and end-stage phases in 45 patients and 42 controls (67). Choroidal thickness was found to be significantly decreased in the end-stage-phase and increased in the acute phase and showed a negative correlation with age and disease duration. Third study evaluated foveal retinal thickness, and perifoveal hypoperfusion areas in 21 patients (68). The area of hypoperfusion in deep capillary plexus was found to be greater than that in superficial capillary plexus in line with what Khairallah *et al*. had previously shown (69).

Vascular involvement

Spanish Behçet's disease registry (REGEB) which has collected data from 20 Spanish hospitals between 2009 and 2015 described clinical characteristics of patients registered with venous thrombosis (70). There were 91 patients (16.7%) with venous thrombosis, of whom 60% had lower extremity involvement and 13.2% had more than one vascular territory involvement and in 6.6% there was concomitant arterial involvement. Thrombotic relapse rate was 19.7%. While being male and having erythema nodosum were found to be associated with venous thrombosis, only CNS involvement in the form of pseudotumour cerebri was found to be associated with thrombotic relapses.

A retrospective survey from Egypt analysed the pattern of vascular involvement in 100 patients (43 M, 57 F) with Budd-Chiari syndrome registered between 2014 and 2016 (71). The most common pattern was hepatic vein occlusion, which was seen in 96 patients in isolated form (n=43) or combined with vena cava inferior stenosis/occlusion (n=53). Four patients had BS and all had isolated inferior vena cava occlusion as we had previously observed (72).

Neurological disease

Uygunoglu *et al*. described the clinical and imaging features of spinal cord involvement 'myelopathy' in BS, which is rare and presents a poor prognostic factor for CNS disease (73). MRIs of 11 patients (9 M/ 2 F) during the acute attacks (n=14) and follow-up (n=9) were studied and 2 distinct patterns were described: 1) a "Bagel sign" pattern: a central lesion with hypo-intense core and hyper-intense rim with or without contrast enhancement which was observed in 13 of 14 acute attacks (Fig. 1 a-b); and 2) a "motor neuron" pattern: a symmetric involvement of the anterior horn cells which was seen in 1 of 14 MRIs. Most of the lesions involved long segments (3 vertebra or more) on the thoracic spine. Concomitant CNS lesions were observed in 12 of 14 acute myelopathy episodes. All patterns cleared with some residual lesions after steroid use and immunosuppressive treatment. Authors suggest that "Bagel sign" represent a venous thrombus in a spinal cord with surrounding oedema and underline that it has not been observed in other forms of longitudinal myelopathy. Similarly, Liu *et al*. described clinical and MRI characteristics of spinal cord involvement in BS (74). They made a systematic review of 17 published cases (13 M/ 4 F) including one from their own clinic. They observed that the spinal cord involvement usually appears late (after median of 10 years). The most common symptoms were sensory disturbance, followed by weakness, sphincter or sexual dysfunction, and pain in the back. Cerebrospinal cell count and protein level were slightly increased. It was extensive involving more than 3 vertebral bodies in 10 cases, and more than half of spinal cord in 8 cases in the sagittal plane.

Ishido *et al*. performed a meta-analysis of 11 published studies (including 184 acute and 114 chronic parenchymal NBS patients) to define distinctive clinical features of acute and chronic forms (75). While the frequency of fever and cerebrospinal fluid cell count were increased in the acute form; sphincter disturbances, ataxia, dementia, confusion, brain stem atrophy on MRI, and abnormal MRI findings in cerebellum were more common in the chronic form. Alghamdi *et al*. described ophthalmological manifestations of BS patients with neurological involvement (76). The French group studied 29 patients with ophthalmological involvement among 217 with neuro-BS in a retrospective single centre study. Thirteen patients had parenchymal neuro-BS, while 16 had cerebral venous thrombosis. Parenchymal type included papillitis, retrobulbar optic neuritis and third cranial nerve palsy. Non-parenchymal type on the other hand included papilloedema, and sixth cranial nerve palsy. All patients were treated with corticosteroids and 23 (79%) received immunosuppressive agents. After 6 months of follow-up, 1 patient became legally blind and 9 had visual field defects.

Breniere *et al*. described 2 BS patients with cerebral sinus vein thrombosis who had concomitant intracranial arterial involvement (77). Both patients presented with headache and symptoms of intracranial pressure increase while arterial manifestations appeared later. One male patient had pericallosal

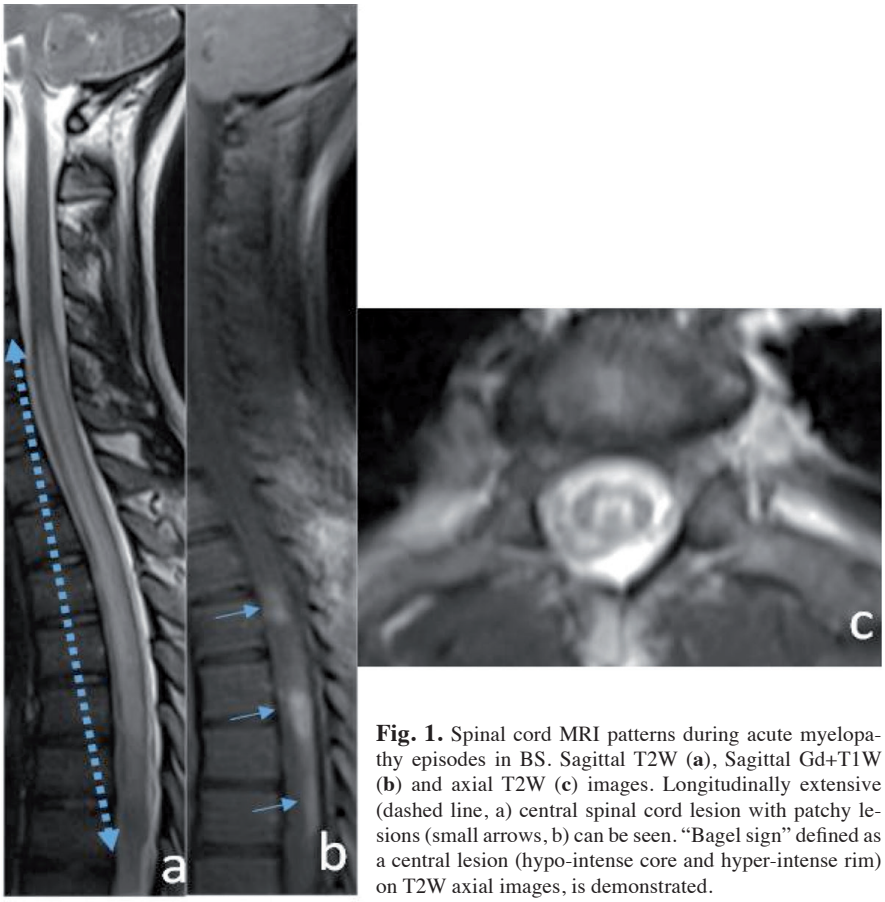

Fig. 1. Spinal cord MRI patterns during acute myelopathy episodes in BS. Sagittal T2W (**a**), Sagittal Gd+T1W (**b**) and axial T2W (**c**) images. Longitudinally extensive (dashed line, a) central spinal cord lesion with patchy lesions (small arrows, b) can be seen. "Bagel sign" defined as a central lesion (hypo-intense core and hyper-intense rim) on T2W axial images, is demonstrated.

arterial aneurysm the other female had right carotid artery occlusion.

Akdal *et al*. defined clinical characteristics of 8 BS patients (3M/ 5 F) who presented with pseudotumour cerebri syndrome and whose MRI's did not show any cerebral venous sinus thrombosis (78). Essential criteria for the diagnosis of pseudotumour cerebri were: 1. bilateral papilledema; 2. lumbar CSF pressure >250mm H2O; and 3. no mass lesion or hydrocephalus on brain imaging. In 4 patients headache was the presenting symptom. All patients responded well to immunosuppressive treatment.

Gastrointestinal involvement

An epidemiological survey showed that the incidence of intestinal involvement appears to be low and has been stable in recent years in Korea (79), a geography with traditionally relatively high incidence. In a nationwide population based study, data of 365 patients with intestinal involvement who had been registered in the Insurance database between 2011 and 2014 were used. The mean annual incidence for intestinal BS was calculated as 0.18 per 100,000. The cumulative rates of surgery at 1 and 4 years after diagnosis were 5.0 and 10.9%, respectively. The hospitalisation rates on the other hand were 27.8 and 32.4%, respectively. The same group analysed the risk factors and outcomes for early readmission within 3 months among patients registered between 2005 and 2016 (80). Among 204 patients, 103 (50.5%) were found to be readmitted within 3 months. Increased disease activity, corticosteroid and opioid use were found to be independent factors for early readmission. The Korean group investigated also the independent risk factors associated with emergency room (ER) visits (81). They observed that 185 patients among 606 with intestinal BS (30.5%) had visited the ER at least once. Lower socioeconomic status, higher comorbidity index, corticosteroid use, higher C-reactive protein, and higher disease activity index for intestinal BS score were found to be independent risk factors for ER visits. Authors identified factors associated with lower gastrointestinal bleeding, as well (82). They compared 66 (11.2%) with acute lower GI bleeding with 132 matched patients without bleeding and found that older age and a nodular ulcer margin were independently associated with bleeding. Re-bleeding occurred in 23 patients (34.8%). Only use of steroids or azathioprine was found to be significantly associated with re-bleeding.

The same group has recently tried to describe a scoring system based on follow-up endoscopic findings that can predict intestinal BS recurrence after surgery (83). A total of 54 patients with intestinal BS who underwent surgery and follow-up colonoscopy were retrospectively investigated. They identified 37 patients who relapsed (61.5%). This was somewhat near the GI relapse rate after surgery recently reported from Turkey as 8/19, 42% (84). These 8 patients were among the 9 who had not received immunosuppressive treatment after surgery. The endoscopic classification model was based on the following classification: 0–no lesions; 1–solitary ulcer <20 mm in size; 2–solitary ulcer ≥20 mm in size; and 3–multiple ulcers. Higher disease activity index and the endoscopic score were identified as independent risk factors for clinical relapse.

Juvenile Behçet's syndrome

Galizzi *et al*. described the baseline data of a nationwide Italian cohort of juvenile BS patients with definitive or probable BS (85). They studied 110 patients (62 M, 48F; mean age: 8.34±4.11 years) from 16 centres. The most frequent major organ involvements were ocular (43.6%), gastrointestinal (42.7%) and neurological (30.9%) involvements followed by vascular involvement (10%). Thirty-two patients (29.1%) fulfilled ISG, 78 (70.9%) ICBD, and 50 (45.5%) PEDBD criteria, whereas 31 (28%) did not fulfil any of the criteria sets. Recurrent oral ulcer was the most frequent clinical manifestation, followed by ocular involvement. Constitutional symptoms were present in 44.5% and recurrent fever in one third.

Audio-vestibular complications

Nada *et al*. determined the types and evaluated the role of auditory evoked potentials and oto-acoustic emissions in early detection of hearing abnormalities in BS (86). A total of 30 patients with BS and 30 healthy controls were studied using pure tone audiometry (PTA), oto-acoustic emissions, auditory brainstem response test and cortical auditory evoked potentials. The study showed that patients with BS have a definite hearing impairment, even in the presence of normal hearing sensitivity, as evidenced by defects in the PTA.

Pregnancy complications

Davutoglu *et al*. evaluated the outcomes of pregnancies in 33 BS patients along with 129 patients with several types of rheumatic diseases seen between 2013 and 2017 (87). The mean maternal age was 31.6±5.2 and the rate of nulliparity was 21.2%. Disease activation occurred in 7 patients. Some of the patients continued to receive medical treatment such as colchicine (n=14), azathioprine (n=4) and steroids (n=3). There was no stillbirth, neonatal death, miscarriages or preeclampsia. Foetal growth restriction occurred in 3 pregnancies, and preterm delivery was seen in 1 patient. The study shows that, obstetric and pregnancy complications in BS are seen with much less frequency compared to that observed in systemic lupus erythematosus and antiphospholipid syndrome.

Triggering or exacerbating factors

It is well known that menstrual cycle triggers multiple autoimmune and several conditions in healthy individuals. A questionnaire survey from our group evaluated the effect of menstruation on disease flare in 200 BS patients, 240 familial Mediterranean fever (FMF) patients and 250 healthy controls (88). The survey showed that in 68% of the patients with BS at least one skin or mucosa lesion exacerbated with menstruation. These were most commonly acneiform lesions (51%), followed by oral ulcers (32%), genital ulcers (25%) and erythema nodosum (21%). Acneiform lesions were also the most common lesion triggered during menstruation among the healthy controls, however, oral ulcers and erythema nodosum were seldom observed. At least 79% of patients with FMF reported attacks of abdominal pain with menstruation, however, this could not be differentiated from dysmenorrhea.

A French study investigated dietary and non-dietary triggers of oral ulcers using a self-administered questionnaire (89). A total of 81 questionnaires out of 101 were evaluated. Fifty patients (62%) admitted that external triggers might be responsible for their oral ulcer recurrences, particularly stress/fatigue (37%) and specific food items (32%). Nuts, pineapple, peanuts, cheese, almonds, and lemons were the most frequently reported foods. Authors suggested that hyper-reactivity might play role in disease mechanism.

Another questionnaire survey from Iran studied 192 patients with BS along with 822 healthy siblings of the patients and 373 healthy unrelated persons and reported that cigarette smoking was not a risk factor for BS (90).

Malignancies

Jung *et al*. collected data of 2402 patients diagnosed with BS between 2013 and 2014 using National Health Insurance claims records to study standardised incidence ratios (SIRs) of overall and site-specific cancers in patients with BS (91). The risks of overall cancer (SIR, 3.54; 95% CI 2.35–5.11 in men and 2.17; 1.58–2.92 in women) and that of solid cancer (3.10; 1.94-4.69 in men and 2.13; 1.52–2.90 in women) were found to be higher in BS than that in the general population. Additionally the risk of myelodysplastic syndrome was greater than that observed in the general population.

Kanamitsu *et al*. retrospectively reviewed records of paediatric-onset BS complicated by myeloid malignancies in Japan between 1995 and 2003 and identified five such patients under 16 years who had presented with intestinal BS and myeloid malignancies (92). All patients were female and had GI involvement, but lacked both major features of BS, such as uveitis and association with HLA-B51.

Reviews

The Cerrahpasa group authored a comprehensive update of the recent advances with a critical standpoint (93). This review directly challenged the MHC-I-opathy concept specifically from the standpoint of globally there are many patients with BS who do not have a MHC-I association and recommended we should be more splitters than lumpers in deciphering the pathogenesis of BS. There have been other comprehensive reviews focusing mainly on neurological (94), vascular (95, 96) and gastrointestinal involvement (97) as well as on oral ulcer (98) and arterial stiffness (99).

Management

Updated EULAR recommendations on the management of BS

A task force consisting of 20 BS experts from different specialties (from 7 European countries and Korea) along with 2 patients, 1 healthcare professional, 1 methodologist and 2 fellows responsible for systematic literature review has updated the 2008 EULAR recommendations for the management of BS (100). Initially, research questions that were not covered in the previous recommendations or that needed update were identified with Delphi approach. The results of a systematic literature review, prepared by the 2 fellows according to a protocol, were then presented to the members of the task force that subsequently finalised the recommendations after thorough discussions and voting. In addition to the updating of the previous recommendations on various manifestations of BS, the new recommendations also contain 5 overarching principles and 1 new recommendation on the surgical management of vascular involvement. Some of the updated recommendations are as follows: one of the overarching principles underlines the importance of multidisciplinary approach for optimal management of the patients. There are suggestions for considering prophylactic immunosuppressive treatment in young men with isolated anterior uveitis and for adding anticoagulants in chronic venous thrombosis and cerebral venous thrombosis as well as

treatment of initial or recurrent episode of acute sight-threatening uveitis with high dose steroids, interferon-alpha or anti-TNF agents. The recommendations also contain a research agenda consisting of different questions that need to be answered in the future for better management of the patients.

Eye involvement

Infliximab and adalimumab are the most frequently used anti-TNF agents for almost all manifestations of BS with refractory uveitis being at the first place. A retrospective study from Italy on 40 patients with uveitis reported retention rates for infliximab at 60 and 120 months as 76% and 47%, respectively (101). The retention rate for adalimumab at 48 months was 64% reflecting the relatively late introduction of adalimumab to BS treatment (102). In another study from the same group there was no difference between the retention rates of adalimumab and infliximab in the treatment of BS uveitis (103). The use of concomitant DMARD's, prior use of biologic therapy and gender differences had no effect on the retention rates. Disease activity at the start of treatment, determined by Behçet's Disease Current Activity Form (BDCAF), was the only item predicting duration of response to adalimumab and infliximab (104).

A retrospective study from Japan assessed the efficacy of infliximab in 38 BS patients with uveitis by using Behçet's disease ocular attack score 24 (BOS24) and fluorescein angiography (FA) scores (105). During follow-up of up to 4 years BOS24 and FA scores improved significantly compared to pretreatment scores.

A retrospective study from our centre showed a changing trend for earlier prescription of infliximab in the treatment of uveitis of BS patients (106). Of the 57 patients receiving infliximab for sight-threatening uveitis between 2003 and 2015, 43 initiated infliximab before 2013 (old group) and 14 initiated infliximab thereafter (new group). The results showed that infliximab was initiated significantly earlier during the course of uveitis in the new group (median: 36.5 months) than the old group (median 72 months). The duration of previous immunosuppressive treatment before initiating infliximab was also significantly shorter in the new group. Baseline visual acuities of both eyes were better at the start of infliximab in the new group than the old group. Infliximab was effective in preserving visual acuity in both groups and attack frequency was significantly lower in the new group. These results are in line with a recent study from Japan on 13 patients (107) and suggest a better visual outcome with earlier initiation of infliximab. On the other hand, the retrospective design of both studies, the few number of patients and relatively short duration of follow-up underline the need for further studies.

Inspired by maintained remissions of rheumatoid arthritis after discontinuing anti-TNF agents and also by long-term remissions of BS uveitis after cessation of interferon alpha some new studies look at the feasibility of tapering or even cessation of anti TNF agents in BS after achieving remission.

A multicentre retrospective study from Spain reported the experience with spacing adalimumab injections in BS patients with uveitis (108). Out of a cohort of 74 patients receiving adalimumab, 65 (87%) achieved ocular remission within a median time of 6 months. Of these, 23 (35%) started to receive adalimumab in prolonged intervals (optimisation group). The decision for prolongation was based on a shared agreement between the patient and the treating physician. The remaining 52 patients continued to use adalimumab at standard schedule (non-optimised group). During follow-up, visual acuity was preserved in both groups and recurrences were seen in 2 and 4 patients in the optimisation group and non-optimised group, respectively and it was possible to stop adalimumab treatment in 4 patients in the optimisation group. Serious adverse effects were seen only in the non-optimised group. Mean adalimumab costs were 50% lower in the optimisation group compared to the other group.

A retrospective study from a single centre in Greece looked at the feasibility of maintained remissions after stopping anti TNF agents (109). In a cohort of 46 BS patients, 29 achieved complete and sustained remission under anti-TNF treatment and had a follow-up of at least 3 years after discontinuation. All patients were refractory to prior treatment with glucocorticoids and immunosuppressives. The main indication for anti-TNF treatment was eye involvement (22 patients). The first anti-TNF agent was infliximab in 27 patients and adalimumab in the remaining 2. All patients except 3 were also receiving concomitant azathioprine. The median duration of anti-TNF treatment was 2 years (IQR: 1.1–2.0 years) at the time of withdrawal. Twelve patients (11 with ocular involvement and 1 with gastrointestinal involvement) remained in long-term remission during a median follow-up of 7.3 years (IQR: 5.5–8.7 years) after withdrawal and 8 were completely drug free. The remaining 17 patients (59%) experienced relapses within a median of 1 year (IQR: 0.6–1.5 years) after withdrawal. Anti TNF treatment was re-instituted in 16 patients and was effective in 14 patients (82%). Four of these patients underwent a second discontinuation with maintained remission for a median of 6 years. The results of both studies seem to be encouraging, but the undulating course of BS, characterised by spontaneous remissions and exacerbations – as respectfully underlined in the Greek study – should always be kept in mind when making decisions for stopping treatment for major organ complications of BS.

Anti-TNF agents are effective for severe BS uveitis but not all patients respond to these agents or they could not be used because of adverse events or loss of efficacy. Two retrospective studies reported the efficacy of tocilizumab, an IL-6 receptor antibody, in severe uveitis of BS refractory to biologic agents (110, 111). The first study from Turkey reported 5 BS patients with uveitis treated with tocilizumab for between 5 and 19 months following inadequate response to infliximab or interferon alpha (110). Tocilizumab was effective in suppressing active inflammation and uveitis attacks in all patients. The second multicentre study from Spain reported 11 patients with

severe uveitis refractory to immunosuppressives and/or biologic agents (111). Treatment with tocilizumab was effective for all ocular outcome measures in all patients with a rapid onset of action. On the other hand, improvement of extraocular manifestations was seen in only 3 patients and in 1 patient tocilizumab had to be stopped because of worsening of arthritis. Different responses of different organ complications to treatment is not new for BS and worsening of mucocutaneous manifestations under treatment with tocilizumab has been reported before (112). Despite this concern tocilizumab may still be an option for severe uveitis of BS when anti-TNF agents fail and awaits further clinical studies validating its place in the treatment of BS uveitis.

Following positive results of a small proof of concept study and a phase II uncontrolled study, the efficacy of gevokizumab (anti IL-1β antibody) added to standard care for reducing the risk of uveitis exacerbations was studied in a placebo controlled, double blind trial in 83 BS patients (40 gevokizumab, 43 placebo) (113). At inclusion all patients were using glucocorticoids either in combination with immunosuppressives (mostly azathioprine or cyclosporine A) or as a single agent (1 patient). The study was terminated prematurely by the sponsor when it was evident that the primary efficacy endpoint - delay in time to first ocular exacerbation - could not be reached. On the other hand, the authors suggest that gevokizumab could reduce uveitis severity, preserve visual acuity and decrease macular oedema leaving the door open for further studies on the suppression of IL-1β pathway in BS uveitis (113).

Vascular involvement

Venous involvement in the form of deep venous thrombosis or superficial vein thrombosis is the hallmark of vascular involvement of BS. Systemic inflammation in the vessel wall rather than a coagulation defect seems to be operative in the development of thrombosis and treatment is based on the use of immunosuppressives rather than anticoagulants. Anti-TNF agents are now used for almost all complications of BS but experience on their effect on venous thrombosis of the extremities is limited.

A retrospective study from a single centre in Italy compared the efficacy of adalimumab with that of classical immunosuppressives (azathioprine, cyclosporine A, methotrexate, and cyclophosphamide) in 70 BS patients having recurrent venous thrombosis of the extremities (114). Adalimumab was used in 35 patients either as a single agent (27 patients) or in combination with azathioprine (7 patients) or methotrexate (1 patient). Glucocorticoids were used empirically. Additionally, 10 patients in the adalimumab group and 11 patients in the immunosuppressive group received oral anticoagulants. Complete response to treatment was defined as clinical and sonographic resolution of venous thrombosis. During a mean follow-up of 26 months clinical response was seen in 97% of adalimumab treated patients and in 66% of immunosuppressive treated patients. The mean dose of glucocorticoids was significantly lower in adalimumab treated patients and the time on treatment was also significantly longer in the adalimumab group. In the adalimumab group 9 patients (26%) discontinued treatment either due to lack of efficacy (7 patients) or adverse events (skin rash). In the immunosuppressive treated group 27 patients (77%) switched to other therapies because of loss of efficacy (23 patients) and adverse events or loss of compliance (4 patients). The use of anticoagulants had no effect in responses of both groups. These results encourage the use of adalimumab in the treatment of venous thrombosis of BS and underlines the need for prospective studies.

A retrospective study reported the course of cerebral venous thrombosis in 7 BS patients after withdrawing anticoagulation treatment while being on treatment with colchicine, steroids and azathioprine (115). Cerebral venous thrombosis recurred in 1 patient 5 months after stopping anticoagulation when he was free of steroids and azathioprine. This observation led the authors to speculate that oral anticoagulation is not a keystone in the management of CVT or in preventing its recurrence.

Haemoptysis is the main symptom of pulmonary artery involvement (PAI) of BS that may be life-threatening and requires prompt treatment. Endovascular embolisation of bleeding aneurysms appears to be a life-saving intervention for the control of hemoptysis reducing the need of surgery. A retrospective study from a tertiary referral centre in Paris reported the outcome of 9 BS patients with hemoptysis who underwent endovascular embolisation along with 8 similar patients collected from the literature (116). Embolisation was successful for immediate control of haemoptysis in all patients. The short-term complications were worsening of pre-existing pulmonary hypertension in 1 patient and development of pulmonary infarction in 2 patients. Following embolisation, 15 patients (88%) received immunosuppressive treatment, mostly with cyclophosphamide combined with glucocorticoids. Recurrence of haemoptysis occurred in 7 patients after 5 months (IQR: 1-12 months) during follow-up and the source of bleeding was determined as enlargement of bronchial arteries due to increased blood flow and pressure in bronchial arterial bed. Embolisation of bronchial arteries was performed in 4 patients and was successful in 2. The 2 patients who were refractory to embolisation underwent surgery, but the outcome was fatal in 1. The overall mortality rate within 1 year was 24% reflecting again the sinister prognosis of PAI.

Recently, our group reported the outcome of 9 BS patients (8 men) who underwent surgery for PAI or its complications between 2000 and 2017 (117). The main pathologies were pulmonary artery aneurysms in 5 patients (bilateral in 3), bilateral pulmonary artery thrombosis, multiple large cavities, bronchiectasis due to saccular aneurysm of descending aorta and massive pleural effusion, each in 1 patient, respectively. Lobectomy was performed in 6 patients, cavity repair and decortication was performed in the remaining 3 patients. Two patients died during follow-up. The first due to hepatic failure as a result of Budd-Chiari 1 year

after the surgery and the second with haemoptysis 3 months after surgery. The median follow-up of remaining 7 patients was 8 years (IQR: 4–11 years). These results are definitely more satisfactory than our previous experience and suggest that surgery may be feasible in selected patients with PAI.

A couple of reviews focusing on the management of BS have been published within the last year, some examples being a systematic review on the management of skin, mucosa and joint involvement and another on the management of major organ involvement, both forming the evidence base for the EULAR 2018 recommendations (118, 119), a review on anti-tumour necrosis factor treatment in intestinal BS (120), on management of vascular BS (121) and on management of BS (122).

Acknowledgement

We thank Hasan Yazici for his critical reading of this review.

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