Review

Behçet's syndrome: a critical digest of the 2014-2015 literature

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ABSTRACT

Several studies were published last year which focused on the epidemiology, immunopathogenesis, genetics, clinical manifestations and management of Behçet's syndrome. Recent epidemiologic studies support the earlier contention that the frequency of BS increases from North to South in Europe, BS is rare in Sub-Saharan Africa, it follows a more severe course among young men, especially if the disease onset is at a young age and that in European countries, the frequency is higher among immigrants from BS prevalent countries compared to locals living in the same environment. The relationship between HLA-B51 and Behçet's was re-emphasised and a functional role affecting cellular cytotoxicity was proposed. Innate immunity was explored and TLR7 copy number variations and nucleic acid sensors of varying inflammasome pathways were studied. Vascular relapse risk is decreased when BS patients are treated with immunosuppressives with or without anti-coagulation rather than anti-coagulation alone. Although rare in the Far East, the clinical picture of the vascular involvement was quite similar to the previously published reports. Interestingly a female predominance among those with cerebral vein thrombosis was noted. Venous claudication is a frequent and severe symptom among BS patients with lower extremity DVT. Budd-Chiari syndrome associated with BS is usually associated with IVC thrombosis. Silent cases exist and have a better prognosis. The mortality rate among the patients symptomatic for liver disease remains high. Methotrexate seems to be effective in the treatment of chronic progressive neuro-Behcet's disease. Renal involvement is an uncommon disorder in BS. Suicidal thoughts are increased among BS patients with severe organ involvement. Work-related disability in BS is high and under-appreciated. Apremilast, an inhibitor of phosphodiesterase-4, was effective in a phase 2, double blind, placebo-controlled study. Adalimumab seems to be effective in severe uveitis of BS even after failure of infliximab. New cytokine inhibitors targeting IL-1 and IL-6 appear to be effective especially for uveitis and CNS involvement refractory to anti TNF agents.

Disease criteria

The diagnosis of Behçet's syndrome (BS) is made by recognising the presence of a number of clinical findings in a patient, since there are no pathognomonic signs, or specific laboratory, radiologic or histologic findings for BS. Similar to several other rheumatologic conditions, this brings the need for disease criteria. A review published last year elaborates on the development and use of criteria sets for BS, as well as other rheumatologic diseases which are actually "constructs" rather than well defined pathologies such as tuberculous arthritis or gout (1). The authors emphasise the misconception of thinking that classification and diagnostic criteria should be different since diagnosis actually is classification for an individual patient, the importance of Bayesian (pretest) probability in formulating criteria and the possibility of increasing pretest probability by preparing subspecialty specific disease criteria and the inclusion of family history in the criteria set, the importance of high specificity compared to sensitivity for a criteria set in order to identify rare diseases correctly, the value of including the absence of certain findings in the criteria set in order to exclude other diseases that are frequently seen in the same setting, and finally the importance of sharing with our patients the fact that our process of diagnosing and making decisions rely on probabilities.

Epidemiology

The differences between geographies regarding the clinical manifestations of BS continue to be puzzling for researches. Several studies are published every year, reporting disease characteristics in a certain geography or a certain ethnic group. During the previous year, there have been reports on BS manifestations from Nigeria and from Azerians living in Iran (2, 3).

BS is known to be rare in Sub-Saharan Africa (4). A recent report from Nigeria showed that 15 patients were diagnosed with BS between 2007 and 2011, in the Lagos State University Teaching Hospital that receives patients from all over Nigeria (2). Nine of these patients were men, 6 were women, mean age at disease onset was 27 and mean age at diagnosis was 33 years. None of the patients had a family history of BS. Eye involvement was frequent among these patients, affecting 12/15 (80%). This may be due to a referral bias due to referral of the most severe patients to this university hospital, or may reflect the difficulty of diagnosis unless a severe organ involvement is present, in an area that BS is not commonly seen and easily recognised. Two of these patients with eye involvement had lost vision. Additionally 2 patients had CNS involvement, 1 patient had deep vein thrombosis and another had superficial thrombophlebitis.

Khabbazi and colleagues reported the demographic and clinical features of 166 Azeri BS patients who lived in Iran (3). There were more men in their cohort compared to women, with a male to female ratio of 1.7. The mean age was 25.8±8.9 years, mean disease duration at the time of diagnosis was 8.6±4.6 years and 4.8% of these patients had a family history of BS. The frequency of ocular involvement was 58%, vascular involvement was 9%, central nervous system (CNS) involvement was 3% and gastrointestinal involement was 0.6% among these patients. There was no difference between men and women regarding the frequency of clinical manifestations. However men with BS had more active disease with significantly higher Iranian Behçet's Disease Dynamic Activity Measure scores (3.1±2.9 *vs*. 1.8±1.3, p=0.002). Additionally, eye involvement was more severe among men. More men had retinal vasculitis (26.9% *vs*. 14.5%, p=0.005) and panuveitis (23.1% *vs*. 8.1%, p=0.008). Overall, 11.5% of their patients had lost vision in 1 eye and 1 patient had lost vision in both eyes.

Another recent report from Iran is the Community Oriented Program for Control of Rheumatic Diseases (COPCORD) study (5). This is a cluster randomised, field based prevalence study that looked at the prevalence of several musculoskeletal and rheumatologic conditions including BS, in Sanandaj (5). In this study BS prevalence was reported as 10 per 100,000 (95% CI 5 to 29). Previous COPCORD studies from other parts of Iran had reported a BS prevalence of 8 per 100,000 (95% CI 4 to 16) in Tehran and 23 per 100,000 (95% CI 8 to 63) in Zahedan (6,7).

The highest prevalence of BS had been reported from Turkey, Istanbul as 421 per 100,000 in a population based field survey and there were 4 other prevalence studies showing prevalences between 370 and 20 per 100,000 individuals (4). Recently a new prevalence study was published. This time, from central Turkey (8). This was a field study where 5218 individuals were screened with a standard questionnaire (8). The prevalence was reported as 17 per 100,000 (95% CI 8 to 33), the lowest prevalence that was reported from Turkey until now. Interestingly familial Mediterranean fever (FMF) is very common in central Turkey, with a prevalence of 0.92% (5). The low Behçet's prevalence in this area compared to other parts of Turkey may be another evidence for separate segregation of BS and FMF and there have been proposals for co-segregation, mainly through an increased frequency of MEFV mutations among the Behcet patients, as well (9).

The prevalence of BS is known to decrease from South to North (4). In two previous prevalence studies from Italy, the prevalence was reported as 3.8 per 100,000 (95% CI 2.0–5.8) in Reggio Emilio in Northern Italy and 15.9 per 100,000 (95% CI 8.9–28.5) in Potenza in the south (10, 11). This time another group from Northern Italy looked at Behçet's prevalence in Brescia (12). The prevalence in Brescia was 4.1 per 100,000 (95% CI 2.9–5.2) confirming the previously observed lower prevalence in the North. However this was not a field survey. The cases that were identified were already diagnosed patients, recruited from the authors' own database or the regional registry for rare diseases. This may have resulted in some underestimation of the prevalence. The authors also looked at the prevalence of BS in the Italian-origin and Non Italian-origin population living in this area separately. Similar to previous reports from France (13) and Germany (14), the prevalence was higher among immigrants (8.5 per 100,000; 95% CI 3.5–13.5) compared to the Italian-origin population (3.5 per 100,000; 95% CI 2.3–4.6). The non-Italian BS patients were first generation immigrants from Morocco, Albania, Egypt and Senegal. Although such studies are important for shedding light on the issue of genetic versus environmental factors in the pathogenesis of BS, data about prevalence among second and third generation immigrants are needed for a more reliable conclusion on this matter.

Age and gender

It has long been accepted that BS patients with a young age at disease onset experience more severe disease and major organ involvement (15). A recent study from Tunisia challanges this finding (16). BS patients with disease onset before the age of 20 were compared to those with disease onset after the age of 40 in a retrospective cohort. There were 81 patients (55 men and 26 women) in the younger onset group and 68 patients (45 men and 23 women) in the older onset group. Cutanous involvement, pseudofolliculitis and vena cava thrombosis were more frequent among younger onset patients and joint involvement was more frequent among older onset patients. The proportion of patients with ocular, vascular and CNS involvement as well as nodular lesions and pathergy positivity were similar between younger and older onset patients. However there was no mention of severity and extent of each type involvement and

having the similar number of patients with each type of involvement does not show that the two groups are similar in severity. Moreover 2.5% of the patients in the young onset group had died compared to none of the patients in the older onset group. HLA B51 positivity rate was similar between the two groups.

It was previously proposed that men with Behçet's syndrome are not free from the risk of major organ involvement, even if they had only mucocutaneous involvement during the early years of their disase (17). This was especially true for those patients with an early age at disease onset. A recent study from Italy also tackled the question of whether being free of major organ involvement during the first years of BS indicates a more favourable outcome (18). In a cohort of 120 Italian BS patients, 62 (34 men, 28 women, mean age 41±6 years) were free of major organ involvement for at least 3 years after diagnosis. Among them, 21 (34%) developed major organ involvement during long term follow-up (mean 8 years). Nine of these patients developed CNS, 9 developed vascular and 3 developed eye involvement. Similar to the Turkish study, the patients who developed major organ involvement were more frequently men (19/21), young (mean age 32±6 years) and those who had a young age at disease onset (20/21).

Gender is another well known prognostic factor for BS. Men with BS have a more severe disease course with a higher frequency of major organ involvement and higher mortality rates. A recent analysis of a German registry data together with a meta-analysis of 52 other datasets confirmed that there are differences in disease course according to gender and showed that male gender was associated with eye involvement, papulopustular lesions, superficial and deep vein thrombosis, whereas female gender was associated with genital ulcers and joint involvement (19). There were some differences between the German registry and the meta-analysis of other datasets, such as the association of male gender with heart involvement in the registry data and association of pathergy positivity with male gender and erythema nodosum with female gender in the meta-analysis of other cohorts.

Epidemiology of BS as a cause of uveitis

BS is one of the leading causes of uveitis in countries with a high BS prevalence, in contrast to other parts of the world. A number of manuscripts were published last year that report the causes and patterns of uveitis in ophthalmology clinics in different countries (20-34). When we reviewed these reports we observed that the frequency of BS as the couse of uveitis among all uveitis cases, is somewhat parallel to the general BS prevalence in that country (Table I). The proportion of BS uveitis among all uveitis was 32.2% in Turkey, 10.5% and 12.4% in 2 different parts of Iran, 12.8% in Lebanon, 8.4% in Saudi Arabia and 8.8% in Japan compared to 2.7% in the United Kingdom, 2.9% in Italy, 2% in Germany, 2.1% in Chile and 0.2% in the United States (central Virginia) (25-27, 29, 30, 33, 21-23, 34, 20). This is more pronounced among the panuveitis cases. BS is the cause for panuveitis in 61% of the patients in Turkey, 48% and 34.3% in Iran, 20% in Lebanon, 17.1% in Saudi Arabia and 16.5% in Japan (25-27, 29, 30, 33). Interestingly, even in countries where BS is not a leading cause of uveitis, the proportion of BS among panuveitis may be high. An example to this is Spain where BS constitutes 5% of all uveitis cases, but 25% of the panuveitis patients (24). Some of these studies also reported the causes among men and women separately, although they did not elaborate on the severity or types of uveitis according to gender. In these studies the proportion of BS among men was higher than that in women in countries with a high BS prevalence. These were 22% among men and 5.9% among women in Lebanon, 15% among men and 3.2% among women in Saudi Arabia and 13.4% among men and 3.2% among women in Japan (29, 30, 33). In contrast to these, frequency of BS among men and women were similar in the UK (both 2.7%) and Spain (6.2 and 4.7%) (21, 24). A few of these studies also looked at the causes according to age of onset of uveitis. In Germany all of the BS uveitis had their onset between the ages of 16 and 64, with no BS patients among earlier or older onset uveitis cases (22). In Lebanon 8.3% of patients whose age of onset of uveitis was less than 16 years, 14.8% of those whose age of onset was between 17 and 60, and 5.5% of those whose age of onset was over 60 years had BS (29). In the Spanish cohort, 22% of all uveitis patients were of non-Spanish origin and the diagnoses were similar to those in their geographic origins for these patients (24). The authors emphasise the importance of globalisation and immigrations that seem to change the epidemiology of diseases in Western countries. This finding points out to the need for caution for recognising BS among ophthalmologists practicing in parts of the world with a lower BS prevalence.

Disease assessment

The lack of validated, generally accepted and widely used outcome measures makes it difficult to compare the results of studies in BS and establish standard management strategies (35). Efforts are continuing to improve this towards developing a core set of outcome measures for BS trials and 2 new outcome measures have been published during the previous year (36, 37).

Bang's group developed an electronic medical report based disease activity index (36). They tested it in 73 Korean BS patients and found a good correlation with Behçet's disease current activity form (BDCAF) (r=0.835) and physician's overall activity assessment score (r=0.782) and a moderate correlation with acute phase reactants (r=0.520 for erythrocye sedimentation rate and r=0.422 for C-reactive protein). The authors report that it takes shorter to complete this index compared to the BDCAF (95 vs 115 seconds). However it should be noted that, the researchers themselves filled BDCAF which is a composite, patient and physician reported index. The fact that this new index is electonic based makes it easy to be integrated with health care systems and easy to use in clinical trials. Some of the disadvantages of this index may be scoring nodular lesions and papulopustular lesions together as skin involvement, scoring arthralgia and arthritis

Table I. Number of Behçet's syndrome patients among all uveitis patients, reported from uveitis clinics in different countries last year.

Country, Years covered, No. of patients, (Male/Female)	Anterior uveitis	Posterior uveitis	Panuveitis	Intermediate uveitis	Total (%)	Total among Men	Total among Women
United States 1984 – 2014 n = 491 (M/F = 213/278)	0/332	0/62	1/71 (1.4%)	0/26	1/491 (0.2%)	NR	NR
United Kingdom 1991-2013 n = 3000 (M/F=1377/1623)	NR	NR	NR	NR	81/3000 (2.7%)	44/1623 (2.7%)	37/1377 (2.7%)
Germany 2012-2013 n = 474 (M/F = 213 / 261)	4/253 (2%)	2/100 (2%)	0/31	3/90 (3%)	9/474 (2%)	7/213 (3.3%)	2/261 (0.8%)
Italy 2004-2013 n = 104 (M/F = 39/65)	NR	NR	NR	NR	3/104 (2.9%)	NR	NR
Spain 2009 – 2012 n = 1022 (M/F = 465/557)	4/534 (0.7%)	11/240 (4%)	39/156 (25%)	1/92 (1%)	55/1022 (5%)	29/465 (6.2%)	26/557 (4.7%)
Turkey 1998-2010 n = 1028 (M/F = 598/430)	42/432 (9.7%)	118/256 (46.1%)	155/254 (61%)	16/86 (18.6%)	331/1028 (32.2%)	NR	NR
Iran 1999-2012 n = 2016 (M/F = 915/1101)	23/865 (2.6%)	6/432 (1.4%)	159/329 (48%)	24/390 (6.1%)	212/2016 (10.5%)	111/915	101/1101
Iran (South) 2005-2011 n = 475 (M/F = 216 / 259)	4/190 (2.2%)	21/133 (15.7%)	34/99 (34.3%)	NR	59/475 (12.4%)	NR	NR
Iraq 2007-2011 n = 318 (M/F = NR)	NR	NR	NR	NR	26/318 (8.2%)	NR	NR
Lebanon 2009-2011 n = 209 (M/F = 91 / 118)	3/53 (5.6%)	6/52 (11.5%)	16/80 (20%)	2/24 (8.4%)	27/209 (12.8%)	20/91 (22%)	7/118 (5.9%)
Saudi Arabia 1998 – 2013 n = 642 (1220 eyes)(M/F = 295/347)	2/450 (0.4%)	4/130 (3.1%)	98/574 (17.1%)	0/66	54 / 642 (8.4%)	83 / 554 eyes (15%)	21 /666 eyes (3.2%)
Thailand 2007-2012 n = 446 (M/F = 206/240)	2/200 (1%)	NR	23/178 (12.9%)	NR	30/446 (6.7%)	NR	NR
Singapore 2004-2012 n = 363 (M/F = 199/164)	NR	NR	NA	NR	10/363 (2.8%)	NR	NR
Japan 2007-2009 n = 295 (M/F = 163/132)	4/105 (3.8%)	0/57	22/133 (16.5%)	NR	26/295 (8.8%)	22/163 (13.4%)	4/132 (3.0%)
Chile 2002-2012 n = 611 (M/F = 256 / 355)	3/247 (1.2%)	4/110 (3.6%)	6/203 (3%)	0/51	13/611 (2.1%)	7/256 (2.7%)	6/355 (1.6%)

together as joint involvement, and not weighing the manifestations when calculating the total score.

The other new outcome measure that was introduced last year is a patient reported mucocutaneous activity index (37). This index includes questions about the number, level of pain and level of functional impairment caused by oral ulcers, genital ulcers and erythema nodosa. Papulopustular lesions are not evaluated as well as patients' self image, which may often be impaired in young BS patients with several nodular and papulopustular lesions. The poor correlation with physician's global assessment for overall status of mucocutaneous manifestations (r=0.15, p=0.037) needs to be elaborated on.

Immunospathogenesis and genetics

HLA-B51 has strongly been related to BS and has widely been replicated in diverse populations with varying ethnic backgrounds. A recent review by Graham Wallace has focused on this relationship and has discussed the possible functional roles of this histocompatibility antigen (38). The presentation of antigen to $CD8^+$ cells has been ruled out since this cell population is not prominent in BS and a specific pathogen or auto-antigen has not been demonstrated. HLA-B51 binding to killer Ig-like receptors *(e.g.* KIR3DL1) on NK cells and the resulting changes in cellular cytotoxicity has been evaluated as a possible mode of action. The mapping of HLA-B51 peptide interaction to six positions around the peptide binding groove and to one position in the signal peptide and the potential role of these areas in interacting with killer Ig-like receptors has been discussed. Additionally the epistatic interactions between endoplasmic reticulum associated aminopeptidases-1 (ERAP-1) that remove NH2 terminal residues from peptide precursors to optimise their length for MHC-1 binding and HLA-B51 have been proposed and the potential role of ERAP polymorphisms that could affect antigen presentation have been considered (38).

A Spanish group performed a replication study on the epistatic interaction of ERAP1 and HLA-B in BS in a Spanish population of 362 patients and 460 controls. They studied 5 single nucleotide polymorphisms (SNPs) related to ERAP1 (rs17482078, rs27044, rs10050860, rs30187 and rs2287987) and looked whether their odds ratios (OR) were higher in patients carrying the HLA-B risk factors (HLA-B51 and B57). They saw that the frequencies of the homozygous minor alleles of all the SNPs were increased among patients and the ORs were higher among the patients with HLA-B risk factors although a statistical significance was absent. They thought that these results were consistent with both an association and an epistatic interaction with ERAP1 and HLA-B (39).

A Dutch group performed a new genome wide association study (GWAS) in a heterogenous BS population of

Western European, Middle Eastern and Turkish origin (336 BS cases and 5843 controls) (40). Genomic Principal Components and Linear Mixed Modelling accounted for corrected population stratification. SNPs associated at genome wide significance mapped to the 6p21.33 (HLA) region as expected. Two potential novel associations on chromosome 6 and 18 were identified and a meta-analysis revealed a relationship with the IL12A variant rs17810546 on chromosome 3 (40).

The results of the study identified SNPs associated at genome-wide significant level mapping to the 6p21.33 (HLA) region. In addition to this, known signal two potential novel associations on chromosomes 6 and 18 were identified, yet with low minor allele frequencies. Extended meta-analysis reveals a GWS association with the IL12A variant rs17810546 on chromosome 3.

Another study tried to independently replicate the findings of four published GWAS for BS (41). The authors tested the allelic and genotypic association with BS of fourteen SNPs in 13 genomic loci (excluding the major histocompatibility complex [MHC], IL10 and IL23R-IL12RB2 which have already been associated with BS in Iranian patients) on 973 patients and 828 controls from Iran and performed a meta-analyses for significantly associated markers. The results of the study reinforces the notion that CCR1, KLRC4, IL12A-ASN1, STAT4, and ERAP1 are of potential interest for susceptibility genes for BS, in addition to the MHC, IL10 and IL23R-IL12RB2 loci.

MiRNA gene polymorphisms may affect miRNA biogenesis and function and, may thus, lead to changes in the expression of hundreds of genes such as NFKB1. Recently, a study from Turkey investigated the association of BS with NFKB1 rs28362491, pre-miRNA-146a rs2910164, and pre-miRNA-499 rs3746444 polymorphisms, as well as the analysis of their single and combined effects on its susceptibility (42). The results of the study demonstrated that homozygous CC genotype and C allele of rs2910164 polymorphism are protective factors against BS, but rs3746444 and rs28362491 polymorphisms in miRNA-499 and in NFKB1 promoter are involved in genetic susceptibility to BS.

Although the association of BS with HLA-B5 was already well established, a number of recent genome-wide association studies in various populations have both confirmed and further looked into this association to individual SNPs both inside and outside the HLA. A recent study examined whether some of these SNPs could be replicated in an Iranian population, where the prevalence of disease is amply documented. Eight SNPs were selected and tested in 552 patients and 417 controls (43). The authors reported that BS in Iran is strongly associated with HLA-B*51, MICA-A6, and the three HLA-linked SNPs. These data further indicate that the robust HLA-B/MICA association may be explained by a single variant (rs76546355) between the two genes.

Fortune's group from the UK studied the expression of suppressor of cytokine signalling proteins (SOCS) in BS. These proteins negatively regulate the JAK-STAT signalling pathway of cytokine induction and affect the production of IFN-gamma, IL-12, IL-23 and IL-6. SOCS1 and 3 mRNA were significantly upregulated in peripheral blood mononuclear cells with BS compared to healthy controls. There were also slight differences among expression patterns between active and inactive disease and in patients with oral ulcers compared to those without. They concluded that SOCS expression was dysregulated in patients with BS compared to controls and in patients with systemic involvement compared to mucocutaneous involvement. The pathologic significance of these findings were not clear (44).

Fang *et al*. explored the association between the copy number variations of Toll like receptor 7 (TLR7), and ocular BS disease in a Chinese Han population (45). The initial stage of the study involved 400 patients with BS, 400 with the Vogt Koyanagi Harada syndrome, 400 with anterior uveitis with or without ankylosing spondylitis and 600 healthy subjects and the second stage enrolled 578 BS patients and 1000 controls. In the first stage, there was a significantly increased frequency of more than one copy of TLR7 in male BS patients and more than 2 copies in female patients. The second stage confirmed the association. The study showed that a high copy number was associated with BS. The study did not address patients who did not have eye disease and did not further comment on gender differences (45).

Another study that explored the role of innate immunity studied nucleic acid sensors of the inflammasome pathways in 9 candidate genes (DDX58, IFIH1, TLR3, TLR7, TLR8, AIM2, IFI16 (Gamma interferon inducible protein), ZBP1, and TLR9) among 371 Spanish BS patients and 854 controls (46). Two SNPs (rs6940 in IFI16 and rs855873 in AIM2) were associated with BS. One haplotype (rs6940T-rs855873G) was identified as a risk factor (OR 1.41, 95% CI 1.06–1.86, p=0.015), and another (rs6940A-rs855873A) as a protective factor (OR 0.65, 95% CI 0.47–0.90, p=0.009). Additionally the steady-state basal IFI16 mRNA expression was haplotype-dependent. This showed that *IFI16,* a cytosolic sensor of dsDNA and mediator of the AIM2 inflammasome-dependent pathway, had a role in susceptibility to BS. It also suggested that AIM2 was also operative in addition to the classsical NLRP-3 inflammasome (46).

One of the pivotal GWAS studies in BS had showed that the dysregulation of IL-10 had an important role in the pathogenesis. A joint Portuguese Iranian group attempted to determine IL10 low frequency variants in a discovery group of 50 Portuguese patients and an additional group of 26 Portuguese and 964 Iranian cases and 104 Portuguese and 823 Iranian controls. Rare IL10 coding variants were not detected in BS patients whereas 28 known SNPs and 5 non-coding variants in five heterozygous variants were found (47).

A study investigated the subclasses and the immunophenotypic profile of peripheral mononuclear cells in patients with BS and assessed its association with HLA B51. Forty patients with BS and 30 controls were enrolled. Patients with active BS showed an increased ratio of CD56 on $CD16^{+}CD56^{+}$ cells, increased absolute numbers of $CD4^{(-)}$

$CD8^{(bright)}$ and $CD4^{(+)}CD8^{(+)}$ cells and an elevated CD19 on B cells. The cellular types were not related to HLA-B51 (48). Micro RNAs are small endogenous non-coding RNAs that are involved in the negative post-transcriptional regulation of gene expression. A recent review summarised the findings in this area. A miR-146a variant, rs2910164 was strongly associated with BS in a Chinese population. miR-155 level was decreased in BS patients with active uveitis compared to controls. Overexpression of miR-155 in dendritic cells promoted the production of IL-10 and inhibited the expression of IL-6 and IL-1 beta. Numerous miRNA studies on BS are ongoing (49).

Table II summarises the numerous polymorphism studies that utilise a candidate gene approach (50-65). They have limited power and their value in deciphering the pathogenic mechanisms of BS are debatable.

Although the cause of BS is not fully elucidated, herpesviruses have long been thought to play a pivotal role in the pathogenesis. Recently, a study investigated the seroprevalence and salivary shedding of herpesviruses in BS compared with recurrent aphthous stomatitis (RAS) (66), showing a high EBV shedding observed in both BS and RAS. Other interesting data are coming from studies that explore predisposition to insulin resistance and metabolic syndrome (MetS) in BS patients. Among these, a recent study evaluated serum salusin-α and salusin-β levels in BS patients and healthy controls and investigated their association with MetS (67). Twenty-five BS patients and 25 healthy controls were included in the study and salusin-α and salusin-β levels were measured in blood samples using ELISA. The results of the study indicated that serum salusin-α level (an anti-atherogenic molecule) was lower, while serum salusin-β level (a pro-atherogenic molecule) was higher in BS patients; this element is of a particular interest since the decrease in salusin-α and the increase in salusin-β levels may contribute to the development of MetS. Other interesting proposals for further research come from studies exploring angiogenic mediator; specifically, a recent study was aimed at assessing angiopoietin-1 (Ang-1) in the plasma of BS patients as well as at analysing its association with clinical, and laboratory parameters of the disease. Although the results did not indicate a significant association among plasma Ang-1 levels and other clinical manifestations or disease activity and severity, plasma Ang-1 levels were diminished in BS patients, especially those with vascular involvement (68).

Finally, an interesting hypothesis came from an Italian study aimed at comparing the gut microbiota structure and the profiles of short-chain fatty acids production in BS patients and healthy control relatives (69). The authors compared the fecal microbiota of 22 patients with BS and that of 16 healthy co-habiting controls, sharing the same diet and lifestyle by pyrosequencing of the V3-V4 hypervariable regions of the 16 rDNA gene and biochemical analyses. The results of the study revealed significant differences in gut microbiota between BS and healthy cohabitants. In particular, they found that BS patients seem to present peculiar dysbiosis of the gut microbiota that correspond to specific changes in microbiome profile. Moreover, a significant decrease of butyrate production in BS patients was demonstrated. Since butyrate is able to promote differentiation of T-regulatory cells, the results obtained, prompted the authors to speculate that a defect of butyrate production might lead to both reduced T-reg responses and activation of immuno-pathological T-effector responses.

Clinical manifestations

Eye disease

A group of ophthalmologists from Saudi Arabia described clinical features of 132 (102 M, 30 F) BS patients with eye involvement seen between 1986 and 2011. Bilateral panuveitis associated with retinal vasculitis was the most common manifestation. About 57% of patients maintained at least 20/50 or better baseline best-corrected visual acuity at final follow-up and were primarily managed with oral corticosteroids and other immunosuppressive agents (70).

Vascular involvement

A multicentre study from Turkey investigated therapeutic approaches in 260 BS patients (224 M, 36 F) with vascular involvement (71). The median follow-up was 48 (range:1–376) months. The majority of the patients had venous involvement (n=231). Immunosuppressive agents were given to 90% for a median of 22 months and anticoagulation to 60% of the patients for a median of 13 months. A second vascular event developed in 33% and third vascular event developed in 7% of the patients. The vascular relapse rate was similar between patients taking only immunosuppressives (29%) compared to those taking immunosuppressives and anti-coagulation combination (22%), (p=0.28) and was significantly higher in patients treated with anti-coagulation alone (92%) (p<0.001). A further multivariate analysis showed again that relapses were only negatively associated with immunosuppressive treatment.

In a similar study, Chinese physicians investigated clinical features of 93 BS patients (77 M, 16 F) with vascular involvement (72). Lower extremity vein thrombosis (74%) was the most common form. Vena cava (30%), pulmonary artery (15.1%), and cerebral vein thrombosis (12.9%), were the least common forms, followed by intracardiac thrombosis (8.6%), Budd-Chiari syndrome (7.5%), and renal vein thrombosis (4.3%). 95% of the patients had multiple thrombosis. Although rare in the Far East, the clinical picture of the vascular involvement was quite similar to the previously published reports. Interestingly a female predominance among those with cerebral vein thrombosis was noted. All patients received glucocorticosteroids and immunosuppressive agents, while 82% also received anticoagulants. After a median follow-up of 14 months (3–63 months), 89 patients improved and 4 patients died.

Our group had previously shown that claudication was significantly more common among BS patients with lower extremity venous thrombosis (LEVT) (73). In a subsequent survey, we reassessed the presence of this venous claudication prospectively by a questionnaire and a treadmill exercise (74).

Table II. Candidate gene approach studies (polymorphisms) in Behçet's syndrome.

Name	Patients	Ethnic Group	Result
IL-10 signalling pathways (JAK1, TYK2, STAT3)	223 patients, 222 controls	Korea	No significant result (10)
IL6-174 G/C	43 patients, 43 controls	Tunisia	No significant result (11)
MMP-9	240 patients, 288 controls	Tunisia	MMP-9 2003 G/A (rs17577) associated with BS, especially in women MMP-9 1721 C/G (rs2250889) is protective (12)
CLEC16A	988 Vogt Koyanagi Harada (VGH), 400 BS, 976 healthy controls (HC)	China (Han)	No significant Result (13)
NFKB1, NFKBIA	89 patients, 190 controls	Turkey	ins/ins genotype and ins allele of rs28362491 more frequent in BS (14)
IL-23 receptor gene	123 patients, 168 controls	Turkey	rs17375018 variant in IL-23R gene causes susceptibility (15)
CD11a, CD11c and CD18	305 patients, 266 controls	Korea	Rs11574944 CC and haplotype rs11574944C-rs2230433G-rs8058823A in CD11a lower in BS, rs2230429CC, rs2929GG and haplotype rs2070946A-rs235326C-rs760456G-rs684G in CD18 higher in BS (16)
CTLA-4 Exon-1 49 A/G	60 patients, 95 controls	Egypt	CTLA-4+49 A allele and A/A genotype more frequent in BS (17).
IL-18	80 patients, 80 controls	Egypt	-607 phenotype different in BS, GG-137 higher in eye disease (18)
TNIP1	656BS, 961 VGH, 1534 HC	China (Han)	No significant result (19).
PTPN2 rs1893217	407 patients, 679 controls	China (Han)	PTPN2 rs1893217 associated with BS (20)
CC receptor CCR5 delta 32	122 patients, 227 controls	Portugal	No significant result (21).
Rho-kinase 1 (ROCK1)	192 patients, 255 controls	Turkey	CC genotype for rs73963110, CT genotype for rs111874856 and TC genotype for rs112130712 increase BS risk (22).
TRAF5, TRAF3IP2	789 BS, 940 VKH, 1601 HC	China (Han)	rs6540679, rs12569232, rs10863888 of TRAF5 and rs13210247 of TRAF3IP2 associated with BS (23)
IL-6 and IL-10	87 patients,97 controls	Egypt	IL-10-1082 G/A related to BS (24)
Vitamin D receptor	50 patients, 50 controls	Iran (Azeri)	VDR f allele and f/f genotype associated with BS (25).

We studied all male 61 patients with LEVT, 40 BS patients without vascular involvement, and 56 healthy controls. We found that 34% of BS patients with LEVT and 5% of BS patients without vascular involvement described venous claudication when assessed with the questionnaire ($p<0.001$). A total of 21% patients with LEVT and 8% with no vascular disease suffered from claudication during the treadmill exercise ($p=0.002$). Finally, we observed that 10% of patients with LEVT had to stop the treadmill challenge because of claudication.

Our group also investigated the clinical characteristics and the long term outcome of 43 (40 M/3 F) BS patients diagnosed as Budd-Chiari syndrome (BCS) (75). We found that 77% had presented with liver-related symptoms while the remaining 23% who were asymptomatic for liver disease, were diagnosed while screening. The median follow-up of these patients was 8 years. A total of 47% had died after a median of 10 months after diagnosis. Those patients who were asymptomatic for liver disease at presentation had a better prognosis. Our study also defined some distinctive demographic and clinical characteristics when BCS due to BS was compared to BCS associated with other causes, such as: male predominance, younger age, early onset during the course of BS, occlusion of the IVC rather than the hepatic veins, the presence of silent cases, increased mortality rate, rarity of portal vein thrombosis, a better response to immunosuppressives rather than anti-coagulation alone, and low success rate of vascular interventions. French colleagues were also interested in BCS (76). In a retrospective survey, they tried to differentiate BCS due to BS from BCS due to other causes (76). They described clinical findings and management strategies of 14 BS patients with BCS and 92 patients with BCS due to other causes. Similar to that found in our study, male gender and IVC thrombosis were found to be closely associated with BS and immunosuppressive treatment with anti-coagulation seemed to be the mainstay treatment.

Ambrose *et al*. (77) looked at the capability of MR in evaluating vein wall thickness in 5 patients with BS and 7 healthy controls in a pilot study. Authors found that thickness and signal enhancement of the popliteal vein as studied by MR was increased in BS patients. An editorial suggested that the method would be promising especially in predicting future vascular involvement however needs to be improved (78).

Neurological disease

Domingos *et al*. described clinical characteristics of 25 (10 M, 15 F) patients with neurological involvement out of 138 BS patients followed in a centre

at Portugal (79). The first neurological manifestation in these patients was headache, followed by diplopia and pyramidal syndrome. Brainstem syndromes were the most frequent manifestations followed by aseptic meningitis. The majority (12/25) had a monophasic course of disease while 9 followed a relapsing-remitting course. When compared to those without, BS patients with neurological involvement had significantly more common vascular and gastrointestinal involvement. Mohamed *et al*. retrospectively studied the brain MRI findings of 68 BS patients diagnosed with neurological involvement seen in a university hospital in Marrakesh between 2004 and 2011 (80). The majority (52/68) had parenchymal form of neuro-Behçet, 12 had vascular form and 4 had normal MRI. The brainstem, cerebral white matter, basal ganglia, internal capsule, thalamus and spinal cord were involved with decreasing order of frequency. The cerebral peduncle was the mainly involved brainstem structure followed by the pons. Hirohata *et al*. investigated the effects of various treatments on the outcome of 37 patients with chronic progressive neurological disease (CPNBD) followed between 1988 and 2013 (81). Twenty-eight of 37 patients with CPNBD (75.7%) received methotrexate, of whom 10 also recived infliximab, while the remaining were treated with high doses of steroids, cyclophosphamide, and azathioprine. Among these 28 patients, none died and only 5 patients progressed to disability with bedridden state, however, among the 9 patients who did not receive methotrexate, 5 died and 3 progressed to bedridden state. Thus, authors concluded that methotrexate significantly improved the survival of patients with CPNBD as well as reducing the rate of progression into bedridden state or death.

Joint involvement

Fatemi *et al*. described clinical characteristics of joint involvement in 430 BS patients out of 2312 seen in a 5 year period (82). The prevalence rate of the joint involvement was 51%. Monoarthritis was the most frequent pattern, and the most frequently involved joints were knees. The attacks were unilateral in the majority. Ankylosing spondylitis was seen in 10%. There was no association between HLA-B5 or HLA-B27 and any type of musculoskeletal involvements. Similar to that found previously (83), pseudofolliculitis was the most common manifestation related to joint involvement. Batmaz *et al*. studied femoral cartilage thicknesses of both knees among 31 BS patients and 31 age matched healthy controls using ultrasonography (84). BS patients were found to have significantly less cartilage thickness.

Renal involvement

Zheng *et al*. retrospectively studied clinical characteristics of 16 BS patients with renal involvement out of 618 hospitalised BS patients in Peking from 1998 to 2012 (85). The presentation of renal disease was chronic glomerulonephritis in 6 patients, renal tubular acidosis in 1, renal artery stenosis in 8 and renal vein thrombosis in 1. Renal biopsy revealed minor glomerular lesions, mild mesangial proliferative glomerulonephritis and chronic tubular-interstitial nephropathy. One patient transformed into IgA nephropathy during the follow-up. Authors concluded that renal involvement is relatively uncommon among BS patients.

Outcome

Ugurlu *et al*. described clinical features and outcome in 368 BS patients (197 M, 171 F) seen in a dermatology clinic (86). As previously observed in several studies, neurological involvement and large vessel involvement had later onset during the follow-up.

Suicidal behaviour

Our group studied the frequency of suicidal ideation among 303 BS patients, 52 ankylosing spondylitis patients and 106 healthy controls (87). Suicidal thoughts, were higher among BS patients with major organ involvement (42%) than those with mucocutaneous involvement (35%) and the control groups. These were also significantly higher in BS group when compared to AS patients and healthy controls. It is suggested that caution is required while managing BS patients.

Work-related disability

British colleagues reported that work-related disability in BS is high and under-appreciated (88). Work change was attributed to particularly oral ulceration on speech.

Reviews

A comprehensive update on pulmonary involvement (89), several reviews about gastrointestinal involvement (90-92), a review about pregnancy (93) and a systematic literature review about the association between BS and myelodysplastic syndrome / trisomy 8 (94) have been published. Finally, an interesting patient with BS was discussed as a difficult case of the week in the New England Journal of Medicine (95).

Management

Apremilast

Apremilast is a novel, oral drug that is currently approved for the treatment of psoriasis and psoriatic arthritis. It is a specific inhibitor of phosphodiesterase 4 leading to increased levels of intracellular cyclic AMP with consequent effects on the levels of various cytokines. The efficacy of apremilast in the treatment of oral ulcers of BS has been recently shown in a double-blind, placebo controlled, phase 2 study (96). The trial enrolled a total of 111 patients who had at least 2 oral ulcers at the time of randomisation with no active major organ involvement during 12 months preceding the study entry. The patients were initially assigned to receive apremilast 30 mg twice daily or placebo for 12 weeks. In the second phase the placebo group was switched to apremilast for 12 weeks and finally all patients entered a 4 week post-treatment observational phase.The primary endpoint of the study was the number of oral ulcers at week 12 and this was met by the patients in the apremilast group by having significantly lower number of oral ulcers than those in the placebo group. The efficacy of apremilast in suppressing oral ulcers was evident at week 2 and was maintained throughout the 24 week treatment period. In line with this, the mean decrease in pain scores for oral ulcers was significantly greater in the apremilast group from baseline to

week 12. A similar response was also seen in the placebo group after having been switched to apremilast at week 12. However, the efficacy of apremilast did not persist after withdrawal and the numbers of oral ulcers started to increase within 2 weeks during the post-treatment phase. Gastrointestinal adverse events such as nausea, vomiting and diarrhoea occurred more frequently with apremilast than with placebo. For now, apremilast appears to be a promising drug for the treatment of oral ulcers of BS but these results should be interpreted with caution because of the short duration of the trial and relatively small number of male patients enrolled in the study. Furthermore, the efficacy of apremilast on other manifestations are still unknown and previous observations on BS patients showing different organ responses to treatment with one particular medication preclude easily extrapolation of the effect of apremilast on oral ulcers to other manifestations of BS (97).

Anti-TNF agents

An observational multi-centre study involving 38 uveitis centres in Spain reported the experience with anti-TNF treatment in 124 BS patients with refractory uveitis defined as with partial or no response to high dose corticosteroids and at least one conventional immunosuppressive drug (98). Infliximab (mostly at a dose of 5mg/kg every 6-8 weeks) was the first biologic agent in 62% of the patients and adalimumab (40 mg eow in most cases) in the remaining 38%. Anti-TNF treatment was combined with conventional immunosuppressives in 99 patients (80%). Switching between biologics either because of treatment failure or toxicity was done in 9 patients (6 infliximab and 3 adalimumab) during follow-up. Treatment with anti-TNF agents was effective in controlling intraocular inflammation and in increasing the best corrected visual acuity. A corticosteroid sparing effect was also observed. After 1 year of follow-up, complete control of uveitis was achieved in 68% of the patients. The treatment was stopped in 6 patients but was started again in 3 because of re-activation of uveitis. Anti-TNF treatment was usually well tolerated but necessitated withdrawal in 3 patients because of serious adverse events (malignancy in 2, military tuberculosis in 1).

Adalimumab is being increasingly used in the treatment of inflammatory uveitis of systemic diseases including BS. The results of a retrospective study from Italy suggest that adalimumab might be effective for severe and refractory uveitis of BS even after failure of infliximab (99). In this study adalimumab decreased the numbers of uveitis attacks and increased the best corrected visual acuity in 12 patients including 8 who had been switched from infliximab. A steroid sparing effect during adalimumab treatment was also evident. After a mean follow-up of 21 months all patients but one (92%) achieved remission of uveitis in at least one eye. There was a trend suggesting a better response to adalimumab among TNF alfa blocker naive patients compared to those switched from infliximab but this was not statistically significant.

Based on a systematic review of published literature until May 2013 and using the grading of recommendations criteria, an expert panel consisting of a subcommittee of the Executive Committee of the American Uveitis Society recommended the use of infliximab and adalimumab as first or second line corticosteroid sparing therapy for BS uveitis and infliximab as first or second line therapy for acute uveitis exacerbations (100). In response to a criticism the authors explained that their purpose in these recommendations was medication-centric rather than disease-centric and they did not take the efficacy of alternative biologics such as interferon-alpha into consideration (101).

Emerging cytokine inhibitors

There is no doubt that the use of anti TNF drugs has revolutionised the treatment of BS patients and especially those with severe and refractory eye involvement. On the other hand, increased experience has also shown that these agents, although being effective, are not a panacea for various complications of BS, thus indicating the need of new treatments. In line with this the numbers of case reports or small case series treated with new biologic agents targeting other cytokines are increasing in the literature. Among these cytokines interleukin-1 (IL-1) and interleukin -6 (IL-6) appear as promising targets in the treatment of BS. Accumulated experience with new biologics in BS has been the subject of 2 comprehensive reviews recently. (102, 103).

Anakinra, gevokizumab and canakimumab are the most frequently used anti-IL1 agents and they appear to be especially effective in the treatment of severe and refractory uveitis of BS. As is the case with anti-TNF agents switching between anti-IL1 agents also seems to be feasible. Furthermore, these drugs appear to have a favourable safety profile in terms of significantly lower tuberculosis reactivation, bringing a considerable advantage over TNF blockage for patients living in endemic areas for tuberculosis (102). On the other hand, the case of a patient developing deep vein thrombosis while being in clinical remission under canakinumab therapy makes us to think again the different organ responses of BS to a single medication (104). Based on the experience of limited numbers of case reports, the anti IL-6 antibody tocilizumab seems also to be promising for BS patients with refractory uveitis and CNS involvement (105-107). For now, anti-IL1 and anti-IL6 agents should be reserved only for patients who are refractory to or not appropriate for the use anti-TNF agents but it would be not surprising if we see the change of this point of view in the near future with the collection of new data on these agents.

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