Review

Behçet's syndrome: one year in review 2025

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ABSTRACT

Behçet's syndrome (BS) is a variable-vessel vasculitis with multiorgan involvement and heterogeneous clinical manifestations. A list of studies were published on BS last year including studies that explore the epidemiology of BS in different parts of the world, role of potential immunological biomarkers in major organ involvement phenotypes, genome wide association studies, studies on micro RNAs, toll like receptors, neutrophil function and epigenetics that added to our understanding of the pathogenesis, studies on imaging and clinical findings that aim to improve diagnosis, differential diagnosis, and monitoring of each organ involvement, as well as studies on management, especially focusing on the role of TNF inhibitors compared to conventional immunosuppressives. The aim of this review is to provide a critical digest of the studies on BS published during 2024.

Epidemiology

Behçet's syndrome (BS) commonly starts early during the second or third decade and the first manifestation is usually oral ulceration. Men display more severe disease with increased frequency of eye, vascular and nervous system involvement and a worse prognosis. Late onset BS, that is defined as onset of symptoms after the age of 40 is less frequent and may show clinical and prognostic differences. A recent systematic review explored the disease characteristics and frequency of such patients (1). The authors identified a total of 13 cohorts reporting on late onset patients from Turkey, Greece, Iran, Lebanon, Israel, Algeria, Tunisia, Morocco, Korea, China, and Taiwan. Among the 8524 patients in these cohorts 7% had late-onset BS and 56% of them were men. Interestingly, there was no difference between men and women regarding frequency of organ involvement in late onset patients. When they compared late onset patients with early onset patients in those studies, the frequency of vascular involvement, eye involvement, and erythema nodosum were significantly less frequent among late onset patients.

A study from Israel used data from their Health Maintenance Organisation covering 55% of the country, to explore the changes in the incidence of vasculitidies over time between the years 2007 and 2021, especially related to the COVID-19 pandemic (2). The adjusted annual incidence of BS decreased from 6.3 (95% CI 3.0–13.5) to 1.0 (0.5–2.5) per 100,000 and the relative risk decreased by 0.90 (95% CI 0.85–0.94). The COVID-19 pandemic was not associated with a change in the incidence. A similar decrease was observed in the incidence of giant cell arteritis (GCA) and IgA vasculitis, whereas the incidence of Takayasu's arteritis, AAV, and cryoglobulinaemia did not change. This study is in line with studies from other countries that suggest a decrease in the frequency of BS (3). The main hypothesis to explain this difference was improved hygiene, based on the possible role of microorganisms in the pathogenesis of BS in susceptible individuals. However, the similar decrease in GCA and IgA vasculitis brings the question of whether other factors may also be responsible for this change.

A multicentre study analysed all patients with BS registered in 8 centres in Karnataka state of South India (4). Among the 72 patients registered in this study, the men to women ratio was 1:1, mean age at disease onset was 37.7 years with a diagnostic delay of 18 months. The percentage of patients who fulfilled ISG criteria was 50% and revised ICBD criteria was 70.8%. HLA B51 was positive in 60% of the 45 tested individuals. In this cohort,

the frequency of oral ulcers was 80.6%, genital ulcers 50%, skin lesions 47.2%, musculoskeletal manifestations 31.9%, ocular manifestations 55%, vascular involvement 12.5%, nervous system involvement 6.9%, and gastrointestinal (GI) involvement 1.4%. It is interesting that the frequency of GI involvement is quite low, similar to that observed in the Middle East, rather than the frequency in the Far East countries, which is reported as high as 30% (5). Organ involvement rates were also different from a previous report from Northern India. Vascular involvement was observed in 34.5%, musculoskeletal manifestations observed in 70.7%, and gastrointestinal manifestations in 5.2% of that cohort (6).

A study from Shanghai reported on the epidemiologic features of 1216 patients over the age of 15 who were referred to a BS centre affiliated with Fudan University between 2012 and 2022 and who fulfilled ISG or ICBD criteria (7). Majority of the referrals were from East China. The frequency of oral ulcers was 95.9%, genital ulcers 82.6%, erythema nodosum 47.8%, pseudofolliculitis 35.8%, uveitis 16.4%, GI involvement 34.5%, vascular involvement 15.5%, cardiovascular involvement 11.0%, nervous system involvement 10.9%, and joint involvement 26.7%. An analysis of clinical manifestations according to gender showed that cardiovascular involvement (RR 2.47), vascular involvement (RR 1.89), uveitis (RR 1.48), and pseudofolliculitis (RR 1.41) were more common among men, while genital ulcers (RR 0.81) and erythema nodosum (RR 0.85) were more common among females.

Take home message

- Frequency of late onset BS was 7% with less vascular involvement, eye involvement and erythema nodosum compared to early onset BS, and 56% of late onset BS were men with no difference between men and women regarding frequency of organ involvement (1).

Disease assessment

A new index was developed for assessing ocular damage specific for Behçet's uveitis (8). This index provided standardised grading of damage with very good inter- and intra-observer reliability. The index consists of 5 grades based on vascular changes, visual acuity, and damage in the retinal tissue, choriocapillaris and choroid. Patients with only venous sheathing in the peripheral veins are graded as 1; patients with venous sheathing that progressed centrally towards the optic disc as well as pigment alterations in the macula and/or pallor of the optic disc are graded as 2; patients with venous sheathing in the entire posterior segment with occluded ghost vessels, focal and diffuse visible permanent tissue damage localised to the retina, choriocapillaris level, and choroid and severely impaired vision are graded as 3; patients with generalised retinal vascular attenuation and atrophy, diffuse appearance of ghost vessels, abnormal macular appearance and complete optic atrophy, pigment alterations and atrophic changes at the choriocapillaris level, and severe visual impairment are graded as 4; and finally patients with end-stage structural damage in both anterior and posterior segments or phthisis bulbi, with or without light perception are graded as 5 according to this index.

Take home message

- A new index for ocular damage was developed specifically for patients with Behçet's uveitis (8).

Immunopathogenesis

Inflammatory endothelial activation is a prominent feature of vascular involvement in BS and it is usually accompanied by a thrombotic tendency. Recent data suggest an association between ABO blood groups and thrombotic vascular disease in those carrying non-O (A, B, and AB) groups. In particular, a retrospective study (9) was conducted on 411 BS patients with available ABO blood group data. The results of this preliminary study show the potential contribution of ABO blood groups to the vascular-BS phenotype and suggest an increased risk for vascular BS in association with non-O blood groups.

As the most numerous immune cells in circulation, neutrophils play a key role in the response to insults. While associative data hints at a connection between neutrophil variations and the differing susceptibility to inflammatory diseases between sexes, the underlying mechanisms are still unclear. Recently, a study from China (10) found that dysregulation of two unconventional neutrophil subsets, interferon-α responsive and T cell regulatory, leads to male-biased incidence, severity, and poor prognosis of BS uveitis. This discovery was made through a combination of single-cell RNA sequencing analysis, neutrophil-specific genetic knockouts, and transfer experiments. Further data (11) identified a potential pathogenic role of plasma-derived exosomal SHP2 deficiency in facilitating neutrophil activation and suggested that SHP2 might be an immunoprotective factor in BS uveitis.

The need to better define the pathogenesis of the neurological involvement in BS continues to encourage studies on this aspect. In the last year, interesting studies (12) suggest that IL-6 may contribute to the production of IL-22 by T cells leading to the exacerbation of inflammation and damage within the CNS of neuro-BS patients; moreover, intrathecal production of IL-6 seems to have a role in the pathogenesis of chronic progressive neuro-BS (13). Moreover, cerebrospinal fluid (CSF) IgA levels were significantly increased in neuro-BS compared to non-inflammatory neurological diseases, suggesting that IgA may play a role in the pathogenesis and the IgA index might be useful as a diagnostic marker for neuro-BS (14).

IL-6 seems to be associated also with other major organ involvement (15). In a Japanese multicenter prospective cohort of 260 patients, clustering analysis revealed that patients who did not achieve remission despite treatment with tumour necrosis factor inhibitors (TNFi) had high serum inflammatory cytokine levels while elevated IL-6 was associated with inflammatory major organ events. In addition, the potential mechanisms associated with different phenotypes were recently investigated (16) in a Turkish study aimed at exploring the expression of innate and adaptive immunity-related cytokines in BS patients with active ocular, vascular and

mucocutaneous involvement. The study supported the involvement of both innate and Th1-predominated adaptive immune responses across all BS phenotypes. Interestingly, the IL-17 and Th17-related immune responses appear less prominent in ocular BS, which may explain the ineffectiveness of IL-17 blockade in treating ocular BS.

In the framework of a growing attention for the role of cutaneous lymphocyte antigen (CLA)+ regulatory T cells (Tregs) in autoimmune diseases, a recent study tried to clarify the impact of CLA+ Tregs on BS (17). Peripheral blood samples from 107 BS patients and 114 healthy controls (HCs) were collected and the number of CLA+ Tregs, natural killer cells, B cells, and several subtypes of CD4+ T cells were assessed using flow cytometry and compared between patients and HCs. Notably, BS patients with arterial aneurysms had CLA+ Treg cell deficiency. Moreover, the proportion of CLA+ Tregs in BS patients increased with glucocorticoids and immunosuppressants.

Take home messages

- Growing data indicate that neutrophils may have a pathogenetic role in BS (10).
- IL-6 seems to be associated with the presence of major organ involvement in general and may play role in the pathogenesis of neuro-BS (12).
- BS patients with arterial aneurysms had CLA+ Treg cell deficiency, while the proportion of CLA+ Tregs increases with corticosteroids and immunosuppressants (17).

Genetics

A number of studies on genetics that enhance our understanding of BS pathogenesis were published (Table I). A recent study investigated genetic susceptibility to BS, particularly its intestinal involvement, through a genome-wide association study (GWAS) and human leukocyte antigen (HLA) analysis (18). HLA-B51 remained the strongest genetic marker for overall BS. Novel susceptibility loci for BS included NPHP4, TYW1–AUTS2, SEMA6D MUC22 and KCNIP1. HLA-B46:01 was identified as a significant genetic marker for intestinal BS, but not for BS without intestinal involvement. It showed stronger binding affinity to Mycobacterial peptides compared to HLA-B51:01, suggesting a potential link between Mycobacterium exposure and intestinal BS. It was more common in East Asian populations, possibly explaining the higher prevalence of GI involvement in these regions. It was proposed that identifying genetic markers like HLA-B46:01 can aid in early detection, prevention, and management of intestinal BS. Limitations included the relatively small sample size for intestinal BS especially in the Japanese validation cohort, the exclusion of Turkish datasets from HLA analysis that limited generalisability and the absence of the exact pathogenetic mechanism implicated in this association (18).

ElMonier *et al*. introduced a novel competing endogenous RNA (ceRNA) network and investigated the regulatory role of long noncoding RNAs (lncRNAs) MIAT and PVT1 in BS through their interaction with microRNAs (miRNAs) miR-93-5p and miR-124-3p, and their downstream effects on mRNAs SOD-2 and MICA (19). BS patients showed increased levels of PVT1 and miR-93-5p, and decreased levels of MIAT, miR-124-3p, SOD-2, and MICA compared to healthy controls. BS patients had significantly higher serum TNF-α levels, which correlated with the studied RNAs. ROC analysis revealed that MIAT, miR-93-5p, and miR-124-3p had high diagnostic power, with the highest efficiency achieved by combining MIAT and miR-93-5p or PVT1 and miR-124-3p with SOD-2 or MICA. MIAT and PVT1 acted as ceRNAs, regulating miR-93-5p and miR-124-3p, respectively, which in turn affected the expression of SOD-2 and MICA, contributing to BS development. The study suggested these RNAs could serve as biomarkers for early diagnosis, risk assessment, and personalised treatment of BS. Limitations included the small number of cases studied (70 patients and 30 controls) confined only to an Egyptian population, the absence of a mechanistic depth and limited therapeutic exploration (19).

Wang *et al*. investigated the association of genetic polymorphisms in the long non-coding RNA (LncRNA) C1RL-AS1 and the PTPN6 gene with ocular BS in Han Chinese, among 1011 ocular BS patients and 2305 HC (20). Genotyping was performed using the iPLEX gold system. The rs4013722 polymorphism in LncRNA C1RL-AS1 was significantly associated with ocular BS, particularly in male patients. Male BS patients showed decreased frequencies of the AG genotype and A allele, and increased frequency of the GG genotype. The rs4013722 polymorphism was also associated with skin lesions in BS patients, especially in males. No significant association was found between PTPN6 gene polymorphisms (rs759053, rs7310161, and rs741090) and ocular BS. The association of rs4013722 polymorphism with BS was observed in males but not in females, possibly due to the smaller sample size of female patients. Only a few polymorphisms were studied, and the mechanism underlying the association remained unclear. Further studies are needed to confirm findings in other ethnic populations and explore additional SNPs (20).

Tadayon *et al*. investigated the association between Toll-like receptor 9 (TLR9) genetic variants rs187084 and rs352140 and BS among Iranians (21). The study included 205 BS patients and 207 HC, analysing TLR9 SNPs using PCR-RFLP. rs187084 AG and AG+GG genotypes, and rs352140 CT and TT+CT genotypes were significantly more frequent in healthy individuals, suggesting a protective role against BS. Healthy males showed higher frequencies of rs187084 AG+GG genotype and G allele, while healthy females had higher frequencies of rs352140 CT and TT+CT genotype. rs187084 AG genotype and G allele were associated with an increased risk of genital ulcers in male BS patients, despite their protective role against BS overall. A-C haplotype was more frequent in BS patients, while G-C haplotype was more common in healthy controls. The findings differed from studies in Japanese, Chinese, and Tunisian populations, highlighting the role of ethnicity, environmental factors, and clinical

Table I. Studies on genetics.

Author, year	Main focus	Key findings / contributions
Jung, 2024 (18)	GWAS & HLA in intestinal BS	HLA-B51 remains the strongest genetic marker; HLA-B*46:01 strongly linked to intestinal BS (esp. East Asians). Suggests role of mycobacterial exposure. Limitations: no Turkish cohort, small sample size.
ElMonier, 2024 (19)	lncRNAs & ceRNA network	MIAT↓ and PVT1↓ regulate miR-93-5p/miR-124-3p → affect SOD-2, MICA. Potential biomarkers for early BS diagnosis and personalised treatment. Limitation: small Egyptian cohort (70 patients).
Wang, 2024 (20)	LncRNA C1RL-AS1 & PTPN6 SNPs in ocular BS	rs4013722 polymorphism linked to ocular BS, esp. males; associated with skin lesions. No PTPN6 link. Limited to few SNPs; unclear mechanisms.
Tadayon, 2024 (21)	TLR9 variants	rs187084 and rs352140 may have a protective role agains BS; haplotypes differ by ethnicity. rs187084 G allele increases the risk of genital ulcers in males. Limitations: modest cohort, no serum TLR9 measured.
Zou, 2024 (22)	Neutrophil transcriptomics (WGCNA)	Altered oxidative stress, interferon signalling, excessive inflammation. Hub genes (IL1B, CXCL8, OAS3, etc.) may be biomarkers/targets. Limitations: small (10 patients), no functional validation.
Özkılınç, 2024 (23)	Epigenetics of HLA-B51	Lower HLA-B promoter methylation in familial BS leads to higher HLA-B51 expression. Epigenetic role in pathogenesis. Limitations: small sample, no longitudinal/therapy data.
Sota, 2025 (24)	HLA-B51 and ocular disease	HLA-B51 positivity increases the risk of retinal vasculitis, even in NIU (non-BS). Early aggressive treatment improves outcomes. Biologics effective. Limitations: registry variability, risk of NIU later reclassified as BS.
Burleigh, 2024 (25)	Monogenic mimics of BS	WES found 29% of patients with suspected BS had monogenic diseases mimicking BS (HA20, ISG15, CVID, TRAPS). Non-monogenic cases: 36% HLA-B51+. Emphasises genetic testing, esp. in low-BS prevalence regions.

heterogeneity in genetic associations. Although the study included 205 patients and 207 controls, larger sample sizes could improve statistical power and generalisability. The study did not measure serum levels of TLR9, which could provide direct evidence of its role in BS pathogenesis (21).

Another study investigated the molecular mechanisms underlying neutrophil dysfunction in BS using weighted gene co-expression network analysis (WGCNA) on transcriptome data from neutrophils of 10 BS patients and 10 healthy controls (22). The researchers identified eight gene modules associated with BS. Turquoise Module was involved in oxidative stress responses, including hydrogen peroxide and reactive oxygen species with hub genes that included IL1B, CCL4, and IDO1. Blue Module was associated with inflammatory responses and external stimuli with hub genes that included CXCL8, CD27, and FASLG. Brown Module was linked to type I interferon signalling and antiviral responses with hub genes that included OAS3, RSAD2, and IFIT3. Neutrophils in BS exhibited altered oxygen metabolism, haemoglobin function, enhanced inflammatory responses, and dysregulated type I interferon signalling. Elevated levels of pro-inflammatory cytokines and chemokines suggested excessive neutrophil activation and tissue damage. They inferred that identified hub genes and pathways may serve as biomarkers or therapeutic targets for BS. Small sample size and cross-sectional design limited generalisability and causal inference. Functional validation of hub genes was also missing (22).

A study explored the role of epigenetic regulation, specifically DNA methylation, in the pathogenesis of BS, focusing on the HLA-B51 locus (23). The HLA-B51 allele was significantly more frequent in BS cases (both familial and sporadic) compared to HC, supporting its genetic association with BS. Lower methylation levels in the HLA-B promoter region were observed in familial BS cases compared to unaffected relatives and HC. Sporadic BS cases also showed slightly lower methylation levels compared to HC. HLA-B51 expression was significantly higher in BS cases (both familial and sporadic) compared to HC, suggesting its involvement in disease pathogenesis. A negative correlation between promoter methylation and HLA-B51 expression was observed in sporadic BS cases. The study highlighted the potential role of epigenetic mechanisms, such as DNA methylation, in regulating HLA-B51 expression and its contribution to BS development. Familial and sporadic BS cases possibly had distinct genetic and epigenetic factors influencing disease mechanisms. The small sample size, lack of longitudinal data, and the absence of an analysis of potential effects of past treatments on methylation levels were limitations (23).

The AIDA group did a detailed study analysing the impact of the HLA-B51 allele on uveitis and retinal vasculitis, particularly in the context of BS and non-infectious uveitis (NIU) unrelated to BS (24). It compared three groups: NIU unrelated to BS positive for HLA-B51, BS-related uveitis positive for HLA-B51, and BS-related uveitis negative for HLA-B51. Retinal vasculitis was significantly more prevalent in pa-

tients with NIU positive for HLA-B51, irrespective of BS diagnosis. BS-related uveitis patients negative for HLA-B51 were less prone to develop retinal vasculitis. No significant differences in visual acuity were observed between the groups after statistical corrections. Early aggressive treatment may improve visual outcomes, but treatment delays were noted in BS patients negative for HLA-B51. Long-term structural complications (*e.g.* cataract, macular oedema, optic nerve atrophy) were similar across all groups. Macular oedema was the most common complication, contributing to visual impairment. Anterior uveitis was more common in NIU patients positive for HLA-B51. Panuveitis was more frequent in BS-related uveitis. HLA-B51 positivity was associated with a severe disease course and increased risk of retinal vasculitis, even in NIU patients without BS. HLA-B typing was recommended for NIU patients to identify those at risk for severe ocular disease progression. Biologic agents such as TNFi were used in a significant proportion of patients, showing promising results in managing uveitis. Limitations were lack of detailed descriptions of retinal vasculitis characteristics, and variability in data quality due to the registry-based nature of the study. The probability of the potential reclassification of NIU cases as BS in the future also raised concern (24).

Burleigh *et al*. investigated the genetic basis of BS using whole-exome sequencing (WES) and a custom-made genetic workflow to identify monogenic mimics in a UK cohort (25). The study developed a robust genetic analysis pipeline combining virtual gene panels, exomiser prioritisation, somatic variant analysis, and copy number variant detection. This approach efficiently identified clinically actionable variants. 29% of patients had monogenic diseases mimicking BS, including haploinsufficiency of A20 (HA20), ISG15 deficiency, common variable immune deficiency (CVID), and tumour necrosis factor receptor-associated periodic syndrome (TRAPS). These cases were not HLA-B*51 positive. Among non-monogenic cases, 36% were HLA-B*51 positive, supporting its role as a genetic risk factor for polygenic BS. White British patients were more likely to have monogenic outcomes, suggesting genetic testing may be particularly important in populations with lower prevalence of polygenic BS. The cohort may have been biased toward early-onset or severe cases, as most patients were recruited from specialist centres. This could overestimate the prevalence of monogenic mimics in the general BS population. The study focuses on a UK cohort, and findings may not be applicable to populations with higher prevalence of polygenic BS, such as those in Eastern countries (25).

Özgüler and Nowatzky reviewed recent findings from "-omics" studies in BS and highlighted advancements in genomics, transcriptomics, proteomics, and metabolomics, providing insights into disease pathogenesis, risk loci, biomarkers, and inflammatory pathways (26). Genomics studies showed susceptibility loci such as HLA-B/MICA, SLCO4A, and DDX60L linked to organ-specific involvement (uveitis, neurological, gastrointestinal), sex-specific genetic effects with higher genetic risk in male BS patients, and epistatic relationship between HLA-B51 and ERAP1-Hap10 that increased disease risk. Transcriptomics studies suggested that neutrophils and macrophages played key roles in BS pathogenesis, with activation of NF-κB and MAPK pathways. Sex-specific differences in neutrophil subsets were noted, with males showing higher inflammatory responses. Th17 cells and antigen-presenting cells were contributors to inflammation. Proteomics studies suggested that plasma-derived extracellular vesicles and exosomes revealed biomarkers for vascular involvement and uveitis. Various analyses highlighted complement activation, NF-κB signalling, and immune effector processes. Metabolomics studies showed that altered carbohydrate, fatty acid, and lipid metabolism were present in BS patients. Integrated microbiome-metabolome studies showed similarities between GI involvement and Crohn's disease. Heterogeneous clinical presentations, lack of consensus on phenotype expression, difficulties in recruiting appropriate control groups and a gap between descriptive data and experimental efforts to understand disease mechanisms were stated as challenges (26).

Take home messages

- Intestinal BS showed special genetic associations suggesting previous mycobacterial exposure (18).
- Various mechanisms of neutrophil dysfunction seem to be operative in BS pathogenesis (22).
- Lower methylation levels in the HLA-B promoter region were observed in familial BS cases (23).
- Advancements in genomics, transcriptomics, proteomics, and metabolomics, provided insights into disease pathogenesis, risk loci, biomarkers, and inflammatory pathways (26).

Clinical findings

Eye involvement

A number of studies evaluated the role of different imaging methods on diagnosis and monitoring of Behçet's uveitis (BU). Kabalıoğlu *et al*. demonstrated a strong correlation between wide-field fluorescein angiography (WF-FA) leakage scores and laser flare photometry (LFP)-flare values in BU patients (27). The findings suggest that elevated LFP-flare may serve as a non-invasive biomarker for subclinical inflammation, offering a potential monitoring tool beyond standard clinical observation (27). In a study that explored the role of microperimetry (MP) in the long-term follow-up of patients with inactive BU, although visual acuity and central macular thickness remained stable, MP parameters correlated positively with OCT findings (28). Reduced MP values were linked to photoreceptor and retinal pigment epithelium (RPE) damage, supporting the method's consistency with both functional and structural assessments (28, 29). Şahin *et al*. examined optic nerve function in BS patients with isolated optic disc hyperfluorescence on FA (30). They reported significantly reduced contrast sensitivity in these patients, indicating that fluorescein angiography, even in asymptomatic individuals, may assist in early detection of inflammatory optic neuropathy when combined with contrast sensitivity testing (30).

There were also a number of studies on clinical predictors of visual severity and outcome. Uçar *et al*. found that among BS patients presenting with vitreous cells (VC) at diagnosis, 22% developed posterior uveitis (PU) within two years, significantly more than in those without ocular findings (31). Additionally, the presence of anterior uveitis alongside VC was an independent risk factor for developing PU (OR 5.03, 95% CI 1.37–18.47), underscoring the need for close monitoring in these patients (31). A study evaluated the relationship between disease burden and health-related quality of life (HRQoL) in BU (32). They found that higher Ocular Damage Index (ODI) scores, severe ocular pain, and lower subjective visual scores were significantly correlated with poorer HRQoL, highlighting the psychosocial burden of chronic ocular inflammation (32).

These studies emphasise the growing role of multimodal imaging in detecting subclinical inflammation and monitoring structural-functional changes, while also highlighting the importance of early clinical indicators and patient-reported outcomes in predicting disease progression and impact on quality of life.

Skin and mucosa manifestations

Folliculitis was significantly associated with pathergy positivity, while other mucocutaneous lesions showed no significant associations (33). Serum procalcitonin (Pct), but not salivary Pct, may serve as a potential biomarker for monitoring oral mucosal flares in BS (34). BS appears to predispose to endodontic pathology through systemic inflammation. Frequency of apical periodontitis was 5.8 times higher than controls especially in active disease (35). BS patients with periodontal disease particularly those with vascular involvement had altered salivary and gingival crevicular fluid levels of IL-1β and nitric oxide compared to controls (36). Patient-centred outcome measures can help tailor care strategies in oral manifestations (37).

Vascular involvement

In a head-to-head comparison of BS and Hughes-Stovin syndrome (HSS) patients, two syndromes were found to be comparable with regard to several demographic, clinical and histopathological features, suggesting that HSS is in fact a vascular phenotype of BS (38). Pulmonary artery aneurysms (PAA) were more frequent in HSS, while in-situ pulmonary artery thrombosis (PAT) was more characteristic of BS. In a recent cohort of 153 BS patients isolated PAT was found to be the most frequent abnormality, whereas PAA were rare (39). A quarter of asymptomatic male patients showed segmental or subsegmental PAT despite normal acute phase reactants suggesting silent pulmonary vascular involvement. PAT was localised to peripheral or segmental branches and characterised by non-occlusive, chronic, non-embolic thrombi (40). A pilot study found that optical coherence tomography was effective in characterising disease-specific pulmonary artery wall morphology and offers a promising tool to differentiate BS, Takayasu arteritis, and chronic thromboembolic pulmonary hypertension (41). Among 25 BS with Budd-Chiari syndrome, mild elevations in systolic pulmonary artery pressure were common, but no cases with severe pulmonary hypertension were detected (42).

Nailfold capillaroscopy was found to have potential in identifying patients with vascular involvement (43).

Ağaçkıran *et al*. demonstrated increased inferior vena cava wall thickness in BS patients compared to healthy controls, suggesting that vascular inflammation in BS extends beyond peripheral veins (44). A Brazilian study showed that vein walls are significantly thicker in BS patients compared to controls and the thickness correlated with previous vascular events, but vein wall thickness measurement with ultrasound is not a reliable diagnostic tool for BS due to its low sensitivity and specificity (45).

Epicardial adipose tissue (EAT) thickness was significantly increased in BS patients compared to controls, while carotid artery intima-media thickness (CIMT) showed no significant difference (46). These findings suggest EAT could serve as an early subclinical atherosclerosis marker. Vascular involvement was associated with increased left ventricular outflow parameters suggestive of arterial stiffness, but not with changes in CIMT or hypertension (47). Wang *et al*. identified hypertension in 9.2% of BS patients, primarily due to renal artery involvement, with secondary complications such as hypertensive retinopathy and cardiac dysfunction (48).

Nervous system involvement

Dincses *et al*. emphasises the importance of careful differential diagnosis to avoid misclassification of neurological involvement in BS (49). Among 116 BS patients who were referred for neurological evaluation, only 25% met diagnostic criteria for neuro-BS, while 26% had alternative diagnoses, including primary headache syndromes and multiple sclerosis. In another study of 120 participants, primary and secondary headaches were equally prevalent in BS patients and HC (36.7% each) suggesting that headache could not be helpful in differential diagnosis (50). A diffusion tensor imaging (DTI) study suggests that DTI may serve as a surrogate neuroimaging biomarker for subclinical and overt neurocognitive dysfunction in BS (51). Another study observed that DTI can reveal subtle axonal damage and may explain cognitive dysfunction in parenchymal neuro-BS, offering potential utility for diagnosis and follow-up despite normal conventional MRI (52).

Gastrointestinal involvement

Among 101 Japanese patients with BS, upper GI involvement was present in 18.8%, most frequently affecting the duodenum, stomach, and oesophagus (53). A large retrospective cohort identified non-simple oesophageal involvement and ulcer size >4 cm as independent negative predictors of mucosal healing in GI involvement (54). Gallstones (25.4%) and renal stones (6.3%) were found to be prevalent in a large cohort of patients with GI involvement (55). In a paediatric cohort with GI BS features, 29% had identifiable monogenic or chromosomal variants, including HA20, ELF4 deficiency, and Majeed syndrome (56).

Clinical clusters

Studies exploring clinical clusters indi-

cate that phenotypic variation could be age and gender dependent. Paediatric-onset patients had more frequent neurological involvement and positive family history, while adult-onset patients exhibited more ocular, mucocutaneous, and vascular findings (57). In the Shanghai BS database including 2082 patients, paediatric cohort was distinguished by greater rates of GI involvement, uveitis, folliculitis, and psychiatric disorders, than adult-onset cases (58). Male patients exhibited higher frequencies of papulo-pustular lesions, ocular, and cardiovascular involvement, whereas females showed more joint and mucosal involvement. (59). In a Japanese observational study arthritis appeared to co-cluster with other mucocutaneous features and contributed to poorer quality of life (60).

Psychiatric involvement

Several studies reported high rates of depression, anxiety, fibromyalgia, and sexual dysfunction in BS (51-64). Tsutsui *et al*. also reported limitations in social participation (65).

Socio-economic burden

An Italian cost-of-illness study estimated that the annual societal cost of BS was €21,624 per patient (66). Direct non-health expenses made the biggest contribution. In a multicentre analysis, irreversible organ damage was independently associated with unemployment and reduced work productivity in BS (67).

Mortality

A Korean population-based cohort study of 24,669 BS patients found a 1.28-fold increased all-cause mortality compared to the general population, with highest mortality in the first-year post-diagnosis (68).

Take-home messages

- Non-invasive imaging tools like LFP and microperimetry can detect early or subtle changes not visible on routine exams and fluorescein angiography findings such as optic disc hyperfluorescence may precede clinical symptoms underlining the importance of early imaging (28, 29).
- Vitreous cells at baseline are a red flag for future posterior uveitis; close follow-up is essential (31).
- Pathergy positivity is associated with papulopustular lesions, but not with other mucocutaneous lesions in BS (33).
- Vascular inflammation in BS is widespread and extends beyond peripheral veins (44).
- Pulmonary artery thrombosis, rather than aneurysm, is the predominant form of pulmonary involvement in BS (40).
- Increased epicardial adipose tissue thickness in BS without increased carotid artery intima-media thickness may suggest early subclinical atherosclerosis (46).
- Mimickers of nervous system involvement are frequent in BS and commonly include multiple sclerosis and primary headache syndromes (49).
- Monogenic and chromosomal variants such as HA20, ELF4 deficiency, and Majeed syndrome should be ruled out in paediatric patients with GI manifestations that resemble BS (56).
- Phenotypic clustering in BS is influenced by age, sex, and geography (57-59).
- BS is associated with significant cardiovascular, psychological, and socio-economic burden (61).

Management

A multicentre, open, randomised, head-to-head trial from France compared the efficacy of infliximab (IFX) with that of cyclophosphamide (CYC) in the induction treatment of severe BS (69). This trial randomised 52 patients (37 with vascular and 15 with CNS involvement; 39 of them newly diagnosed) to receive either CYC or IFX. The complete response was similar between both drugs (65% for IFX and 64% for CYC) at week 12, but at week 22 (the primary outcome) complete response was 81% in patients receiving IFX (22 of 27) and 56% in those receiving CYC (14 of 25). The complete response rate for vascular involvement was significantly higher with IFX (94%; 17 of 19 patients) compared to CYC (56%; 10 of 18 patients). Among patients with CNS involvement, the complete response rate with IFX was still higher (63%; 5 of 8 patients) than that of CYC (57%; 4 of 7 patients) but not statistically significant. The small sample size is an obvious handicap for proper interpretation of these study results. There was no difference regarding severe adverse events between the groups, while mild/moderate adverse events were more frequent with CYC. It seems that IFX will replace CYC as the first line drug in the induction treatment of severe manifestations of BS. However, it would be important to know differences in treatment response between different types of vascular involvement (such as between pulmonary artery aneurysms or thrombosis, peripheral artery involvement, or venous thrombosis), between different types of nervous system involvement (such as between parenchymal brain involvement and cerebral venous sinus thrombosis) and between men and women in general.

A multicentre, randomised, single blind study compared the efficacy of IFX and adalimumab (ADA) in BS patients with mainly active mucocutaneous manifestations refractory to previous treatment including colchicine, glucocorticoids, azathioprine, and cyclosporine-A (70). The study included 40 patients (28 men, 12 women) with a relatively old age (mean: 46.8 years) and 18 were randomised to ADA and 22 to IFX. The main outcome of the study, response of mucocutaneous lesions at 6 months was met by significantly more patients in the ADA group (94% *vs*. 64%, respectively; p=0.023). Time to response was also significantly shorter with ADA (median 42 days) compared to IFX (152 days) (p=0.001). Monotherapy or concomitant treatment with immunosuppressives did not make a difference in the efficacy of both drugs. In conclusion, this study, albeit with small number of patients, adds further evidence to the efficacy of monoclonal TNFi in BS.

A randomised, single-blind, head-to-head trial from England randomised 74 BS patients with active symptoms in one or more organ systems compared the efficacy of interferon-α2a with IFX between the years 2016 and 2020 (71). Both drugs were found to be

equally effective with similar improvements regarding the primary outcome (improvement in Behçet's Disease Activity Index (BDAI) at 12 weeks) and secondary outcomes (improvement in individual organ systems at 24 weeks). Head-to-head trials are few in BS and unfortunately, as in this example, some become redundant in many parts of the world, since interferon-α was withdrawn from the market.

Another randomised, single blind, head-to-head trial from China compared the efficacy of cyclosporine-A, interferon-α2a and ADA, each combined with steroids in the treatment of active uveitis in 270 BS patients with a long duration of uveitis that was not adequately treated (90 patients in each group) (72). The primary outcome, standardised annualised relapse rate at month 6 was found to be significantly more frequent with cyclosporine-A compared to ADA. Interferon α2a was not inferior to ADA and also not superior to cyclosporine-A. The occurrence of relapse was earlier with interferon α2a and cyclosporine-A compared to ADA. On the other hand, at month 6, more than 90% of patients in each group still had active retinal vascular involvement in at least one eye while the improvement in best corrected visual acuity was similar in each group. Patient selection by including patients who were still active, but had no permanent eye damage despite being treated for more than 2 years before study entry and the use of concomitant high dose glucocorticoids limit the interpretability of the results.

A multicentre, retrospective study compared the efficacy of ADA (25 patients), IFX (15 patients) and certolizumab (CZP; 10 patients) in the treatment of BS patients with cystoid macular oedema over a period of 2 years (73). Patients in the CZP group had significantly longer duration of uveitis and had used other TNFi before. The main outcome, improvement of macular thickness, was similar in all 3 groups. The study suggests that CZP might be an option in patients with severe uveitis.

A retrospective study of 110 BS patients with pulmonary artery involvement (PAI) that were followed-up in a single centre in Turkey between 1990 and 2023 proposed that anticoagulant therapy when added to immunosuppressives might decrease the relapse rate of PAI (74). PAI was diagnosed by using computed tomography pulmonary angiography (CTPA). The majority of the patients had PAT (94.5%) and only 9 (6.6%) had PAA with 32 patients (29%) being asymptomatic at the diagnosis of PAI. During follow-up, relapse of PAI was detected in 4 patients (12.5%) in the asymptomatic group and in 27 patients (34.7%) in the symptomatic group with repeat CTPA. Anticoagulant treatment was initiated only in 10 patients (31%) among the asymptomatic group and in 51 patients (65.4%) among the symptomatic group. It is not clear how many of the relapsed patients had received anticoagulant treatment. The study also lacks information whether patients labelled as relapsed had relevant clinical symptoms. Furthermore, no information exists about the percentage of patients undergoing repeat CTPAs as well as number of CTPAs per patient. We definitely need high quality studies before adding anticoagulant treatment to patients with PAI, the most lethal and feared complication of BS.

As a general issue the lack of separate analyses for men and women in RCTs in BS is an important shortcoming. This is especially crucial for BS due to the differences in disease severity, frequency of organ manifestations, and potential differences in treatment responses between the sexes (75).

Take home messages

- Infliximab may potentially replace cyclophosphamide as the first line treatment for vascular and central nervous system involvement of BS.
- Accumulating data suggest that interferon-α2a, which is withdrawn from the market in many countries, can be replaced with TNFi.
- Prospective studies are needed to understand to place of anticoagulants added to immunosuppressives in the treatment of vascular involvement.

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