Meeting Report

Highlights of the 17th International Conference on Behçet's syndrome

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The 17th International Conference on Behçet's Disease was held in Matera, Italy between 15th and 17th of September 2016 under the auspices of the International Society for Behçet's Disease. The president of the conference was Professor Ignazio Olivieri.

There were 270 participants, including rheumatologists, gastroenterologists, dermatologists, ophthalmologists and epidemiologists. Twenty-six oral and 125 poster presentations, in addition to 29 plenary lectures, were presented.

Epidemiology

In the opening plenary session H. Yazici emphasised that Behçet's syndrome (BS) is a construct-disease with varying disease presentations at different geographies. This makes the formulation of a universal disease classification/disease criteria set very difficult. The same consideration assumes further importance in basic science work, especially in genetic association studies. A decrease in the prevalence and severity of BS over the last decades has previously been reported by different groups. A Tunisian study reported a less severe course in a decade (1) and a Japanese group reported that the frequencies of complete type syndrome, the frequency of patients with genital ulcers and HLA-B51 positivity have decreased whereas gastrointestinal involvement increased in recent years (2). A prospective study in young, male BS patients without major organ involvement showed that after a mean follow up of 47 months 4/35 (11%) of the patients developed major organ involvement. This is somewhat lower than that reported in historic cohorts, but this may be because they defined young as below the age of 35, compared to 25 in earlier studies (3). Dilşen reported non-oral apthous beginning BS patients were at higher risk for major organ involvement (4). A Japanese study found a positive correlation between smoking rate and the prefectural prevalence of BS in contrast to autoimmune diseases and Takayasu's arteritis (5). Finally, the first epidemiologic study of BS in Jordan reported an estimated prevalence of 66/10000 among hospital workers (6).

Pathogenesis

Various cytokines were identified to be associated with BS, however their role in the pathogenesis and more importantly as therapeutic targets still wait to be elucidated. In a study which looked at a panel of 25 cytokines in active and inactive BS patients together with healthy controls, a key role for interleukin (IL)-6 and tumour necrosis factor (TNF) cell activation was suggested. However, interestingly, these were more pronounced in inactive BS patients. Additionally, they showed increased IL-26 level in active BS patients supporting the role of Th17 pathway (7). A study on serum cytokine profile during infliximab (IFX) therapy for BS-associated uveitis showed that most of the Th1, Th2, and Th17 related cytokines were suppressed after infliximab (IFX) infusion in patients achieving remission with IFX, but not in patients having attacks despite being treated with IFX. They suggested that the measurement of those cytokines may be useful in predicting remission in patients receiving IFX (8). IL17 expression by T lymphocytes was found to be higher in BS than Takayasu's arteritis (9). The researchers interpret the higher IL-17 and interferon (IFN)-γ production by all T lymphocyte subsets in BS as an indicator of increased innate responses and early tissue neutrophil infiltrations

in contrast to Takayasu's arteritis where adaptive responses occur (9). CCR1 and IL-10 were highly expressed by the anti-inflammatory M2 macrophages in BS patients compared to controls (10). This is interesting since susceptible loci encompassing chemokine CCR1 and anti-inflammatory cytokine IL10 genes were identified in a previous GWAS study. Another study reported that monocytes of BS patients facilitated Th1/Th17 differentiation with the help of TRIM21 which is an E3 ligase protein that regulates cytokine production by ubiquitination of transcriptional factors such as interferon regulatory factor family and NF-kB which also has antiviral properties (11). CD16+Vδ2 (12) and CD8+ (13) T cells were also found to be increased in BS patients. γδ T cell population is important in inflammation in many diseases. In BS, β7 but not CLA was found to be a homing receptor of γδ T cell population that produces pro-inflammatory cytokines (14).

Several studies investigated the impact of various single gene polymorphisms (SNP) in BS. There was no association with CXCR1 and CXCR2 SNP and a tendency for the association between IL-17A SNP and gastrointestinal symptoms in a Japanese study. (15). IL-27 gene rs153109 A/G SNP, but not rs181206 T/C was associated with BS in an Iranian study (P2). In a Saudi cohort, IFN-γ (874A/T) SNP, but not IL-6 (174G/C) and TGF-β1 (509C/T) was associated with the susceptibility of BS (16). IL10, CCR1, STAT4 and ERAP1 SNP were frequent in BS patients from Italy (17). TRAF3IP2 SNP was also associated with BS and Vogt-Koyanagi-Harada disease as shown in a Han Chinese population previously (18).

A study attempted to identify loci associated with clinical manifestations through genome wide screening. Several candidate loci were identified for major symptoms and minor symptoms, but interestingly none of those identified for minor symptoms were HLA loci. The relatively low number of patients for this kind of analysis may have hampered the results (19). An immunochip study once again showed that HLA B51 is the strongest association and confirmed the IL10, CCR1, IL12A,

and FUT2 loci. They additionally identified 6 new loci (IL1AIL1B, RIPK2, ADO-EGR2, LACC1, IRF8, and CEB-PB-PTPN1) for BS. Regarding the hypofunctional FUT-2 structural variants, researchers suggested that since fucosylation is required for the regulation of commensal microbiota, this finding may support the role of microbial pathogens in BS pathogenesis (20). Another study showed that carrying HLA-B51 and being homozygous for the ERAP1 haplotype pointed out to a substantial risk for BS (OR 10.96, 95% CI 5.91 to 20.32) (21). The ERAP1 association was also confirmed in a small group of Italian BS patients (2).

Multiparameter cell analysis by machine learning algorithms which enables analyses of flow cytometry data in a novel manner was presented. This technique seems to be promising in distinguishing diseases with similar aetiology (23).

The role of infections in the pathogenesis of BS had been discussed since the condition was originally described. However, a specific pathogen has not been identified. In this conference 2 microbiome studies showed differences in the fecal, oral (24) and salivary (25) microbiota of BS patients compared to healthy controls. No change was reported in this bacterial community structure after oral health evaluation (25). The role of microbiome was also discussed during the plenary lecture on "immune response and tissue-specific factors" and the decreased diversity of the organisms in BS rather than differences in species was emphasised. A study from Japan tested the hypothesis of hypersensitivity against streptococci in BS. The skin prick test with self-saliva, sterilised self-saliva, and saline was performed in 22 BS patients and controls. The skin prick test with self-saliva was more sensitive than the conventional pathergy test. Sterilised self-saliva showed a less response compared to self-saliva. There was stronger response to self-saliva compared to sterilised self-saliva and no response to control saline in BS patients. Among the controls, patients with RAS had a weaker response and patients with herpes simplex virus and healthy controls had no response to their own saliva (26).

Clinical findings

Skin, mucosa and joint involvement

The association of poor oral hygiene with oral ulcers in BS is well known. A retrospective study that evaluated the effect of oral hygiene education reported better periodontal indices among BS patients who were under regular follow-up for oral hygiene compared to those who were not (27). The same group also reported that low drug use adherence was associated with oral disease activity, oral health-related quality of life (QoL) and female gender (28). An English group found an association between oral disease activity and serum lipopolysaccharide levels which is a surrogate marker of increased gut permeability (29).

The role of dietary and non-dietary factors (stress/fatigue, dental care, tooth brushing, menstruation, infection) as triggers of oral ulcers was studied using a self-reporting questionnaire. Fatigue/stress and food, especially sour items were the most frequently reported triggers. Since these food stuff are histamine-rich, the authors considered a possible hypersensitivity mechanism to histamine (30).

The specificity of location, number and difference according to age of papulopustular lesions for BS was challenged in a study that included 155 BS, 57 rheumatoid arthritis (RA) patients and 101 healthy controls. Papulopustular lesions on the legs seemed to be the most specific finding for BS. Number of lesions tended to decrease as the patients' age increase in all groups, but lesions on the legs persisted even after the age of 50 among the BS patients (31). In a study that looked at the relationship between menstruation and mucocutaneous lesions 56% of the 150 patients reported an association with at least one symptom, most commonly papulopustular lesions (50%) (32). In a study from Iran, a positive pathergy test was correlated with mucocutaneous lesions, gastrointestinal and neurological involvement and negatively correlated with eye involvement (33). A study from Korea showed that bone scintigraphy may be helpful in the diagnosis of joint involvement in BS (34). An Italian group evaluated the patterns

of musculoskeletal involvement among their 59 patients and reported that oligoarticular involvement was the most common pattern (35).

Eye involvement

The need for a set of diagnostic criteria for ocular BS to confirm the diagnosis in patients with extraocular manifestations, to prevent misdiagnosis in patients with other types of uveitis, to administer early and appropriate treatment to patients with uveitis as the initial or only manifestation of BS and to include patients with incomplete manifestations or with only ocular disease into clinical studies was discussed. The details of a Delphi exercise to reach consensus on such criteria was presented.

Three studies favoured the use of optical coherence tomography in the evaluation of eye inflammation. One proposed the measurement of subfoveal choroidal thickness (SCT) as a clinical indicator of subclinical ocular inflammation in BS patients without eye disease (36), the second found a correlation between flares and SCT and central macular thickness (37) and the third reported outer plexiform layer elevation as a surrogate marker for history of posterior ocular attacks (38). A controlled study failed to show an association of osteopontin levels with eye involvement (39).

Vascular involvement

In a study that compared post-thrombotic syndrome (PTS) and its impact among BS patients with deep vein thrombosis (DVT) to that among patients with DVT without BS, a higher number of relapses, worse quality of life, but less severity and similar PTS findings were observed among BS patients. Anticoagulation did not seem to decrease PTS among vasculo-Behçet's syndrome (VBS) patients (40). The authors also prospectively followed the same cohort and found no significant change in QoL scores except for mental component of SF-36. However, the initial visits of VBS patients were after a mean follow-up of 74 months of post-DVT (41). A Tunisian group showed that BS patients with DVT had more frequent unusual localisations of their DVT and more recurrences and less concomitant thrombotic risk factors, such as obesity, bed rest, surgery, trauma compared to idiopathic DVT (42). A survey of 100 BS patients with cerebral venous sinus thrombosis (CVST) with a median follow up of 11 years showed that in 48% of these patients CVST occurred before or at the onset of ISG fulfillment. Additional vascular involvement was observed in 59 of the patients and 32 of them developed after CVST. Relapses were rare (n=6) and ophthalmologic complications were observed in 17 (34%) and sensorineural type hearing loss in 4 (8%) of the 50 patients who could be evaluated for these lesions. The authors recommended the examination of the jugular veins by cervical MR-angiography in addition to cranial MR-venography and suggested CVST as a risk factor for future vascular involvement (43). A Tunisian group reported a favourable outcome for superior and inferior vena cava thrombosis with immunosuppressives (44). Vascular involvement was reported in 28% of Tunisian BS patients and males, patients with a positive pathergy and a history of erthyema nodosum had a higher risk (45). A Turkish study reported 12 BS patients with vascular involvement who underwent positron emission tomography/computed tomography (PET/CT). They suggested PET/CT may be helpful to investigate the presence of medium and large size arterial activity, but not in venous involvement (46). A Korean study demonstrated that composite graft aortic root replacement (ARR) had a more favourable outcome compared to bioprosthesis ARR (47). The prospective study of young, male BS patients without major organ involvement mentioned above suggested that a low baseline flow-mediated dilatation, a marker of endothelial dysfunction may be a predictor of major organ involvement (3). BS patients with a history of thrombosis had higher numbers of microparticles expressing tissue factor and lower numbers of microparticles expressing tissue factor pathway inhibitor than those without (48). Fibrin marked resistance to plasmin degradation in BS patients when compared to healthy controls. There was also an altered fibrinogen structure and impaired fibrinogen function that were found to be associated with neutrophil activation. This study may be an explanation why immunosuppressives are more effective than anticoagulants in the treatment of thrombus in BS. Lack of diseased controls was a limitation. Moreover, these findings should be assessed in other inflammatory diseases.

Nervous system involvement and psychiatric disorders

A study of cognitive function in chronic progressive neuro-Behçet's syndrome (NBS) patients showed that cognitive dysfunction was frequent in these patients and cannot be explained by brainstem atrophy. Magnetic resonance imaging revealed a significant decrease in brainstem area of NBS patients (n=13) compared to those of non-NBS (n=13) and Alzheimer's disease patients (n=6). Additionally, severity of grey matter loss in the hippocampal region was significantly worse in NBS patients. However, there was no correlation between brainstem and hippocampal atrophy (49). An Italian study investigated the differences in brain glucose consumption by PET/CT. When compared to healthy controls (n=17), there was a significant reduction of brain glucose consumption in specific areas of brain in NBS patients (n=6). Again, these abnormalities were not associated with the lesion sites (50). A Tunisian group found a frequency of 31% of cochlear involvement (CI) among 55 BS patients. Patients with CI were older with a late-onset disease and tended to have less vascular disease and more papulopustular lesions compared to patients without CI. However, the clinical relevance of this finding is not clear since none of the patients complained of hearing loss and there was no age matched healthy controls (51).

A study of psychiatric disorders in BS patients showed no correlation between disease activity, organ involvement and psychiatric disorders among BS patients. Surprisingly, bipolar disorder (64%) but not sleep disorders, obsessive compulsive disorder and depression were significantly higher in BS patients compared to controls with

systemic lupus erythematosus (SLE) and hypertension (52). Another study from Russia compared mental disorders in 100 BS and 125 RA patients. Major depression was observed in 79% of BS and 94% of RA patients. Similar to the previous study disease activity and neurologic involvement showed no correlation with mental disorders. Cognitive disorders were observed in 93% of BS patients, and correlated with disease activity and depression scores (53).

Paediatric Behçet's syndrome
Gallizzi presented a cohort of 129 paediatric BS patients collected from an Italian registry. The most interesting finding was a considerable high rate of ocular involvement (41.5%) at the baseline visit (54). A Turkish study including 54 paediatric BS patients reported similar findings regarding gender, mean age at diagnosis, frequent gastrointestinal involvement and HLA-B51 positivity, but differed with a higher rate of venous involvement (13% *vs*. 2%) and family history of BS (31.5% *vs*. 11%) (55). A Turkish group assessed the cognitive function of 9 paediatric BS patients and 9 controls by using evoked response potentials. There was no difference in visual processing, but auditory processing was longer in BS patients suggesting subclinical inflammation in different regions of brain (56).

Life impact
Piga presented data on QoL in BS patients. BS patients had worse QoL than SLE, RA patients and healthy controls. They observed lower scores in the mental but not physical component of QoL questionnaire. The low scores in physical component were correlated with disease activity whereas no findings could be found to be associated with the mental component (57). A study on work disability showed eye and musculoskeletal involvement were the leading causes of working disability. Males were more likely than females to have a fear of losing their job (58). Same group also demonstrated BS patients had more negative opinions about mucocutaneous, musculoskeletal and eye involvement. Females had higher emotional stress due to BS symptoms than males (59).

Comorbidities
A UK study found increased cardiovascular, gastrointestinal, psychological and respiratory comorbidities and lower malignancies in BS patients compared to controls (60). A Tunisian group identified 3 patients with malignancy among 211 BS patients, followed between 2000-2016 (61). A nationwide survey in Japan reported the prevalence of allergic disorders driven by Th2 cells was lower in BS patients compared to general population (62). The prevalence of type-2 diabetes mellitus was found to be similar among BS patients and general population (63). There was a case series reporting 10 BS cases with Takayasu's arteritis within a cohort of around 9000 BS patients followed in one centre (64).

Disease assessment
The challenges in developing a core set of outcome measures for BS was discussed and the results of the first round of a Delphi among BS experts and patients aiming to identify domains, subdomains and outcomes to be assessed in trials of BS was presented (65). A group from UK group reported on a list of needs and concerns of BS patients to improve communication between patients and physicians. Those items will be assessed by healthcare professionals and a group of patients and thereafter the final form will be evaluated in a pilot study (66).
A group from Turkey reported that a validated patient reported outcome measure for mucocutaneous BS called the Composite Index, showed a moderate correlation oral health related quality of life assessed with the Oral Health Impact Profile-14. These 2 measures showed a significant correlation with clinical indices and the researchers recommended their use in clinical trials and routine management of BS patients. (67).
BD ocular attack score 24 was proposed by Japanese ophthalmologists as a useful objective scoring system for evaluation of ocular BD. This score was validated for determining disease activity and assessing treatment response in a Russian cohort (68).

Biomarkers
There are controversial reports on the usefulness of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels in BS except for vascular involvement where high levels are frequently observed. This was replicated in a study from Turkey that showed significantly higher ESR/CRP levels in patients with vascular involvement than in those without. The lowest levels were seen in patients with parenchymal NBS and posterior uveitis (69). On the other hand, a study from Iran reported higher ESR and/or CRP levels in active patients with oral and genital ulcers, neurologic manifestations, joint, eye and vascular involvement compared to in inactive patients (70).
Fecal calprotectin (FC) was explored as a biomarker for gastrointestinal involvement in 2 studies. A study from Korea showed that median FC level was significantly higher in patients with gastrointestinal ulcerations compared to those without ulcerations and in patients with typical ulcerations compared to those with atypical ulcerations. A higher FC was found to be an independent risk factor for predicting gastrointestinal involvement (OR=1.02, 95%CI: 1.002-1.038). The proposed cut-off level was 69 μg/g, but with a low sensitivity (76%) and specificity (79%) (71). The second study from Turkey studied the usefulness of FC for predicting gastrointestinal disease activity. 150 μg/g was used as a cut-off for a positive FC level. All 7 endoscopically proven active patients had a positive FC level while 4/16 patients in remission had a positive FC level. FC seems to be a useful test for ruling out active gastrointestinal involvement in patients with low FC levels. On the other hand, serum calprotectin levels were not helpful (72).
Mean platelet volume (73, 74), neutrophil to lymphocyte ratio (74), and YKL-40 (75) were other reported markers that correlated with disease activity in different types of disease presentation.

Management
Efficacy and safety of several biologic agents including anti-TNFs, interferon-alpha, IL-1 blockers and an oral phosphodiesterase inhibitor, apremilast was discussed.

The 2016 update of the EULAR recommendations for the management of BS and 2 systematic reviews on skin-mucosa involvement (76) and major organ involvement (77) that informed the task force updating these recommendations were presented. The major differences from the 2008 recommendations were the recommendation of monoclonal anti-TNFs in refractory cases with all types of involvement and as first line therapy in severe NBS cases, apremilast as an option for mucocutaneous manifestations and the additional recommendations regarding surgical interventions.

Anti-TNF agents, especially IFX were the most frequently studied drugs. Two studies looked at the timing of the introduction of IFX on the outcome of BS patients with eye (78) and neurologic involvement (79). Both showed a better outcome with the earlier use of IFX. A Japanese multicentre, open-label phase-3 study of IFX for BS patients with gastrointestinal (n=11), vascular (n=4) and neurologic (n=3) involvement who were refractory or intolerant to conventional therapy was presented. Among the 18 patients, 13 achieved complete remission at week 30. Safety profiles were comparable to those in patients with RA and Crohn's disease (80). There were 4 case series on anti-TNF agents (IFX and adalimumab (ADA)) (81-84). Eye involvement was the most common indication for anti-TNF use. All reported beneficial results. However, 5/18 BS patients had serious adverse events in the study from Ireland 1/7 patients developed miliary tuberculosis in the Moroccan study. There was no serious adverse event in the Greek (28 BS patients) and the Italian (12 BS patients) surveys. The Greek study also observed that 68% of the patients had a relapse within 6–18 months after the cessation of anti-TNF and 50% of the patients who discontinued the therapy were still in remission after a mean period of 5 years (84). The co-administration of cyclosporine was reported to be effective and well tolerated in 11 Japan patients (85). Data were presented on the immunogenicity of IFX therapy in BS patients with eye involvement. IFX trough levels were significantly higher in patients without attacks compared to what was observed in those with attacks. Among 3 patients with anti-IFX antibodies, 2 had ocular attacks whereas 5 out of 24 without antibodies had ocular attacks.

A single chain anti-TNF antibody (DLX105) was assessed in the management of 6 BS patients in a 2-week open-label study. The tissue penetration of this drug was considered to be better than other large molecules, such as IFX and ADA. It showed a rapid and strong onset of action after a single dose, but it was tested only on mucocutaneous lesions that tend to have a relapsing-remitting course. Long term controlled data are needed to better assess its efficacy (86).

IL-1 inhibitors were reported to be effective in around half of the patients and well tolerated in a series of 30 BS patients (87). A retrospective survey of 13 refractory BS patients treated with certolizumab showed favourable results (88). A case was presented reporting a refractory case to biologics and having partial remission with ustekinumab (89).

A systematic review of intravenous immunoglobulin (IVIG) in BS patients reported 6 patients successfully treated with this agent (90). An Italian group monitored the plasma cytokines in a BS patient during IVIG therapy. The authors observed a decrease in CXCL8 levels which was shown to be correlated with BS clinical activity and suggested IVIG as a promising agent especially in patients unsuitable for immunosuppressive therapy (91).

Conclusion

In brief, a considerable amount of useful information was presented both in basic and clinical science including aspects of management. On the other hand, it is sobering to note that there were no reports of randomised controlled studies (RCT). This may be related to the relatively low prevalence of BS in many parts of the world and difficulties in funding, as well as lack of standardised and widely accepted outcome measures to be used in RCT which are accepted by regulatory authorities.

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