The 20th International Conference on Behçet's Disease
Hotel Savoy Le Grand, Marrakech, Morocco, 18–20 September 2024

The 20th International Conference on Behçet's Disease took place in Marrakech in September 2024. After the conference was opened by its president, Zoubida Tazi Mezalek, the opening lecture was given by Paul Hasler (Switzerland). Prof Hasler spoke about NETosis in autoinflammation. Neutrophil extracellular traps (NETs) are filamentous strands produced by activated neutrophils that can trap and kill bacteria. Triggers include bacteria, viruses, fungi, autoantibodies and cytokines. NETs are present in placenta during pregnancy and are increased in pre-eclampsia and gestational diabetes. In rheumatoid arthritis (RA), cell-free DNA in the blood serum leads to production of NETs, particularly in patients positive for anti-citrullinated protein antibodies. NETs are also produced in systemic lupus erythematosus (SLE) and in anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis. Activated endothelial cells present during inflammation induce NET formation, leading to cell death (NETosis) and endothelial damage; NETs also form a scaffold for the development of thrombosis. In mice, NETs produced during inflammation have been shown to awaken dormant cancer cells. NET formation is thus probably a major factor involved in infection and cancer, as well as in autoimmune and autoinflammatory conditions where it has organ-specific effects on the kidneys, blood vessels and joints. Interleukin (IL)-8 has been shown to induce NET formation in patients with active Behçet's eye disease, an effect that can be reversed by anti-IL-8 injection in mice with autoimmune uveitis.

Scientific Session 1: Basic science

Session 1 of the conference was devoted to basic science, starting with a special lecture on the immunopathogenesis of Behçet's by Martin van Hagen (Netherlands). Autoinflammatory diseases are caused by an exaggerated innate immune system response resulting in episodes of spontaneous inflammation. In autoimmune diseases, the innate immune system attacks and damages the body's own tissues through production of autoantibodies, as well as triggering the adaptive immune system to activate the inflammatory process. Behçet's has some autoimmune but more autoinflammatory

disease characteristics. The production of pro-inflammatory components of the innate immune response to certain triggers may be a key step in the pathogenesis of Behçet's, with neutrophils representing the main infiltrating cell type. Diseases with both autoimmune and autoinflammatory characteristics, such as Behçet's, psoriasis and spondyloarthritis, have a strong association with certain major histocompatibility complex (MHC)-I alleles (e.g., HLA-B51, HLA-B27) and gene variants of the antigen processing aminopeptidases ERAP1 and ERAP2 that result in altered MHC-I peptide presentation leading to the triggering of autoimmune reactions or MHC-1 protein misfolding leading to inflammation. In Behçet's, ERAP1 may mediate HLA-B51 recognition via NK (natural killer) cells. A better understanding of these processes may contribute to the development of new drugs such as ERAP-1 inhibitors.

Alexandre LeJoncour (France) returned to the subject of NETosis to discuss NETs in Behçet's. Neutrophil activation is key feature of the pathogenesis of Behçet's. NETs have a wide range of effects on tissue cells, macrophages and blood vessels, which are consistent with the lesions and pathophysiology of Behçet's. NETs have been shown to be present in Behçet's, with increased concentrations of soluble NETs being demonstrated. NETs induce vascular injury, enhance thrombin generation leading to thrombosis, and promote macrophage activation resulting in production of pro-inflammatory cytokines (e.g. IL-1, tumour necrosis factor [TNF]). Soluble CD40 ligand is an important mediator of inflammation in Behçet's, promoting neutrophil activation and NET production. Blockade of this pathway using colchicine or steroids has been shown to inhibit NET production *in vitro*, while inhibition of phosphodiesterase 4 (PDE4) by apremilast strongly inhibited NET production in neutrophils from Behçet's patients.

Alessandra Bettiol (Italy) spoke about the microbiome and microbes in Behçet's. The human gut microbiome comprises many types of bacteria, including Gram-positive firmicutes and Gram-negative bacteroidetes, which change depending on factors such as life stage and diet. The microbiome plays an important role in immune and metabolic functions – for example, through the production of butyrate, a short-chain fatty acid that helps to maintain a healthy gut barrier, reduces inflammation and protects against intestinal diseases such as inflammatory bowel disease (IBD). The gut microbiome in Behçet's has reduced diversity of species and reduced Roseburia (a firmicute bacterium), leading to lower butyrate levels. Gut microbiome dysbiosis in Behçet's also involves enrichment in certain Gram-negative bacteria and opportunistic pathogens such as Stenotrophomonas, leading to intestinal epithelia barrier damage, increased oxidative stress levels and induction of NETosis. Possible ways of restoring the gut microbiome in Behçet's include direct re-population through faecal microbiome transplantation, use of prebiotics and probiotics, and dietary supplementation. A small Italian study randomised Behçet's patients to either dietary supplementation with butyrate or a lacto-ovo-vegetarian diet containing starch-rich foods whose fermentation increases butyrate production. Both interventions led to a reduction in reactive oxygen species production, as well as a significant reduction in Behçet's disease activity and corticosteroid use, although no change in microbiome composition was seen. Preliminary results from a larger trial in 55 patients show a decrease in gastrointestinal symptoms

The session concluded with five oral presentations of abstracts. A group from Türkiye showed that biomarkers of NETosis, such as cell-free DNA and serum myeloperoxidase, show changes in association with systemic and local Behçet's disease activity. A Chinese study found that farnesyl pyrophosphate (FPP), a metabolite on the mevalonate pathway that is essential for cell growth and

differentiation, induces neutrophil activation in Behçet's. FPP levels were higher in Behçet's patients than in healthy controls and correlated with disease activity; TNF-α increases responsiveness to FPP, suggesting a novel therapeutic mechanism of TNF inhibitors. A presentation from a French group highlighted a possible mechanism behind the beneficial clinical effects of apremilast in Behçet's, showing that PDE4 is involved in CD8+ T-cell activation, cytotoxicity and proliferation, and that PDE4 inhibition mitigates these effects. A group from Korea studied granzymes, enzymes released by cytotoxic (CD8+) T cells and natural killer cells that trigger programmed cell death. They found that serum granzyme K and granzyme K+ senescent CD8+ T cells were increased in patients with active Behçet's. Finally, a study from the UK showed that an enhanced response to stimulation of γδ T cells in people with Behçet's induces proliferation of B cells into plasma cells with increased autoantibody and inflammatory cytokine production.

Scientific Session 2: Epidemiology and genetics

The first presentation in this session, on epidemiological and genetic contributions to Behçet's, was given by Ahmet Gül (Türkiye). Behçet's is a multisystem disorder with heterogeneous presentations. A patient's phenotype is driven by genetics, with HLA-B51 being the strongest genetic factor. It is thought that environmental triggers such as streptococcal antigens, viruses and trauma lead to a hyper-inflammatory response in people with genetic susceptibility through HLA-B51, other HLA alleles and non-HLA polymorphisms. This response, via innate and adaptive immunity and endothelial activation, results in clinical manifestations. HLA-B51 may be an important factor in determining clinical phenotypes, being positivity associated with many manifestations such as eye involvement, skin involvement and genital ulcers, and negatively associated with gastrointestinal involvement. Weaker associations are seen with other HLA alleles. For example HLA-A26 has been shown to be associated with uveitis in Japanese patients, while Korean studies have found associations of HLA-B46 with intestinal involvement and HLA-A26 with both uveitis and intestinal symptoms. Genome-wide association studies have shown an association between HLA-B51, ERAP1 and Behçet's, with ERAP1 haplotype 10 increasing the risk of Behçet's. Several non-HLA polymorphisms contribute to susceptibility to Behçet's, with inflammatory pathways being shared with spondyloarthritis, Chrohn's disease and other autoinflammatory disorders.

Next Luca Cantarini (Italy) spoke about registries in Behçet's. A few European countries (Austria, France, Germany and Italy) have national Behçet's registries, while the Iranian registry has some impressive publications. The Autoinflammatory Diseases Alliance (AIDA) Network encompasses 262 clinical centres (766 investigators in 47 countries; 109 centres in Italy), 45% of which are actively enrolling patients. Among the active centres, 68% are enrolling patients in the Behçet's Disease Registry. The Network is free to join and is multidisciplinary, with physician-driven collection of retrospective and prospective data. The Behçet's registry includes 16 instruments for collection of demographic, genetic, clinical, laboratory, instrumental and therapeutic data designed to reconstruct the complete clinical history of each patient. As of July 2024, 1100 patients had been enrolled, half of them in Italy. Of these 1100 patients, 599 are male, the mean age at disease onset was 28.8 years and the mean age at diagnosis was 38.8 years. Only 72 patients (6.5%) have a positive family history of Behçet's, and 40.3% are HLA-B51 positive. Almost two-thirds (63.7%) have at least one major organ involvement, with ocular involvement being most common (47.2%). A new AIDA for Patients

Behçet's Disease Registry was launched in 2023, with data collection being entirely patient-driven. Patients can access this registry and enter data on patient-reported outcomes through their mobile devices or computers. The plan is for the data entered by physicians and patients to be integrated; a pilot project is being conducted in Italy in collaboration with the patients' association (SIMBA).

Parvez Haris (UK) asked whether chronic exposure to methanol could be the missing link that explains the higher prevalence of Behçet's in silk route countries. Circumstantial evidence supports the role of environmental factors in Behçet's, but no common environmental factors have been identified in the countries with the highest prevalence. Any such factor would need to have been present from ancient times to the present day. Wine was a common product of the different civilisations that existed in the silk route countries, often used as a medicine as well as for drinking. Advances in distillation led to production of aromatic waters such as rose water and perfumes that were traded on the silk route. These health, hygiene and traditional medicinal products may contain methanol of natural origin or from adulteration. Methanol is a toxic substance that can be present in both wine and herbal extracts. Toxic exposure to methanol is quite common in Turkey. Methanol, on its own or in conjunction with natural compounds from plants, may trigger an inflammatory response directly or through dysbiosis of the microbiome. Methanol toxicity has other similarities with Behçet's, including neurological and ophthalmological effects.

The session finished with oral presentations of four abstracts. An Italian group investigated the epigenetic regulation of thrombo-inflammation in Behçet's and antiphospholipid syndrome, concluding that a signature comprising three circulating microRNAs could discriminate between the two conditions. A study of 878 patients in Korea found that HLA-B51 positivity correlates with symptom completeness from recurrent stomatitis to Behçet's. Another Italian study used data from 1024 patients in the AIDA Network Behçet's Disease Registry to look at the influence of gender on Behçet's phenotype and irreversible organ damage. Male patients were more likely to have irreversible damage over time and to have ocular and vascular involvement, while female patients more often had joint, central nervous system and gastrointestinal involvement. Finally, researchers from Türkiye studied clinical features and phenotypic similarities of patients with familial and non-familial Behçet's, finding that the familial group had a younger age at diagnosis and more genital ulcers and papulopustular lesions; family members tended to have similar phenotypes with respect to erythema nodosum-like lesions, joint involvement and vascular disease.

Scientific Session3: Ocular disease

Moncef Khairallah (Tunisia) began this session by considering what is and what is not ocular Behçet's. Ocular involvement has been reported in between 28% and 70% of people with Behçet's, with Behçet's being the leading cause of uveitis in some countries. Uveitis can be the initial and only presentation of Behçet's in up to 20% of patients. A new algorithm for the diagnosis of Behçet's uveitis provides clues for diagnosis, even in the absence of extraocular manifestations. The algorithm is useful in differentiating between Behçet's uveitis and other forms of non-infectious uveitis, which is essential for early treatment to prevent irreversible vision loss. Typical characteristics of Behçet's uveitis include sudden onset and rapid resolution of an acute attack, bilateral involvement and recurrent inflammatory attacks with chronic residual inflammation. Anterior uveitis is rarely isolated in Behçet's, with most cases having posterior segment involvement. Retinal vasculitis is a hallmark of

ocular Behçet's, with a preponderance of retinal vein involvement. Fluorescein angiography is a key tool for detecting new vessel growth and vascular leakage, while optical coherence tomography (OCT) is the gold standard for evaluating microvascular changes in the macula.

In his talk on evaluation of activity in ocular Behçet's, Bahram Bodagui (France) first mentioned that there are multiple grading systems for intraocular inflammation, including at least four for anterior chamber cells, three for anterior chamber flare, two for vitreous cells, and three for vitreous haze and debris. SUN (Standardization of Uveitis Nomenclature) grades inflammation as grade 0, 0.5, 1, 2, 3 and 4 according to the number of cells (<1 to >50) in the field (1×1 mm slit beam). SUN grades anterior chamber flare subjectively from 0 to 4 (none to intense). Combining these measures allows a patient's uveitis to be classified as inactive, worsening activity, improved activity or remission. OCT is a non-invasive imaging method that provides useful information on macular oedema and has changed practice in recent years. OCT angiography is a new tool that has been used to compare retinal features in patients with Behçet's and healthy controls, showing significant differences in retinal thickness and vessel density. Patients with ocular Behçet's had reduced peripapillary vessel density compared with those with non-ocular Behçet's.

Ilknor Tagal-Tutkun (Türkiye) then gave a presentation on treatment of ocular Behçet's in 2024. A single severe attack of ocular Behçet's can cause irreversible damage and vision loss, while recurrent attacks result in cumulative structural and functional damage. Persistent subclinical retinal inflammation, shown by leakage on fluorescein angiography (FA leakage), results in vision-threatening complications and is associated with a high risk of recurrent attacks. A significant reduction in FA leakage during infliximab therapy has been shown to be associated with a better visual outcome, whereas persistent leakage was strongly related to relapse. Thus, no leakage (a 'dry angiogram') is an important therapeutic target; FA leakage should be checked 3–6 months after starting treatment and every 6–12 months during follow-up. In the conventional therapy era, vision loss could not be prevented in resistant cases of Behçet's uveitis. For example, both azathioprine and cyclosporine have proven efficacy in combination with corticosteroid, but they are not always effective in the long term. In the 2000s, interferon-α was the first-line biologic agent used in resistant cases; however, it is no longer available outside China. A recent Chinese study showed that adalimumab was superior to cyclosporine in Behçet's uveitis, while interferon-α was not superior to cyclosporine (all with corticosteroids). Now, early anti-TNF treatment is considered essential to achieve remission and preserve vision. A Spanish study in 177 patients found that while both infliximab and adalimumab were effective, and infliximab led to more rapid improvement of inflammation, adalimumab achieved greater visual improvement over 1 year. Furthermore, a smaller Spanish study showed that tocilizumab (anti-IL-6) had comparable efficacy to infliximab and adalimumab, and was effective in patients resistant to anti-TNF therapy. Other agents that have shown favourable results in case studies include anti-IL-1 agents (anakinra and canakinumab) and Janus kinase (JAK) inhibitors (tofacitinib and upadacitinib). However, only TNF inhibitors are effective for all manifestations of Behçet's, although new manifestations sometimes develop during anti-TNF treatment. Clinical remission is not a reliable outcome for stopping treatment; a 'dry angiogram' should be the target.

Oral presentations of four abstracts completed the session. One Turkish study investigated the effect of adalimumab treatment on NK cell populations in Behçet's uveitis, finding reduced expression of IL-10 and IL-4, but not IL-17 or transforming growth factor beta (TGF-β); cytotoxic functions of NK cells

were good and were not affected by adalimumab treatment. Another Turkish group reported that femoral vein wall thickness is a useful diagnostic tool to differentiate ocular Behçet's from other inflammatory uveitis, with significant differences seen between 45 patients with Behçet's uveitis and 72 with non-Behçet's uveitis. An Italian group used data from the AIDA Network's Behçet's Disease Registry to show that HLA-B51 positivity increases the risk of both uveitis and vascular retinitis. Finally, a US study found that the Behçet's immune landscape has a near-universal nuclear factor-kappa B (NF-κB)-mediated hyperactivation pattern with upregulation of TNFα signalling across all major cell populations and a superimposed interferon-signature in monocytes in Behçet's uveitis.

Scientific Session 4: Neurologic disease

The final session of the first day began with a presentation by Desmond Kidd (UK) on the clinical features and diagnosis of neurological involvement in Behçet's. Neurological involvement is reported in between 3% of 20% of people with Behçet's, with meningoencephalitis (inflammation of the meninges and brain tissue) accounting for around 75% and vascular problems for 18%. Neurological complications of Behçet's include inflammation in the brain, veins or arteries, headache, and cognitive and psychological symptoms. However, around 85% of Behçet's patients have headaches and most of these are not due to neuro-Behçet's, while cognitive and psychological problems do not necessarily indicate neurological involvement. Inflammation within the brain is most commonly seen in the brainstem (50%) and hemisphere (30%), with 10% occurring in the spinal cord. A magnetic resonance imaging (MRI) scan will show the type of lesion involved. The cranial nerves can also be involved, leading to optic or audiovestibular problems. Inflammation in the veins can result in venous sinus thrombosis, cortical vein thrombosis, intracranial hypertension, headaches, visual changes and stroke-like events. More rarely, inflammation in the arteries can cause headaches, stroke-like events, aneurism formation and brain haemorrhages. Psycho-neuro-Behçet's can involve hemiparesis and sensory loss, dysphasia and mutism, and psychiatric symptoms; MRI scans are normal.

Next, David Saadoun (France) spoke about treatment and outcomes in neuro-Behçet's. The relapse rate in patients with neuro-Behçet's involving the parenchyma is 30%, and the risk of disability or death is 25%. The mortality rate in neuro-Behçet's is 10% compared with 5% in Behçet's overall. Prognostic factors include brainstem or myelopathy presentation, early disease progression, impaired neurological state at diagnosis and increased white blood cells in the cerebrospinal fluid (CSF). The spinal cord is affected in 5–24% of patients with neuro-Behçet's; it usually involves the cervical segment, and the prognosis can be severe. Among patients with vascular neuro-Behçet's, the thrombotic recurrence rate is 30%; other sequelae occur in 30–40% of patients and include blindness, persistent headache and focal neurological symptoms. Therapeutic targets in neuro-Behçet's include interferon-γ and IL-17A, which are seen in the blood and CSF. Acute attacks are treated with high-dose corticosteroids. Cyclophosphamide and conventional disease-modifying anti-rheumatic drugs (DMARDs) such as azathioprine have no effect on mild-to-moderate neuro-Behçet's, although the former can be effective in severe disease. However, cyclophosphamide is associated with serious adverse events. Methotrexate can prevent progression of neuro-Behçet's, while mycophenolate mofetil may be an alternative therapy. TNF inhibitors lead to improvement in most patients, including those with refractory disease, with a complete response seen in around 30% and a partial response in 65%. No difference has been shown between infliximab and adalimumab.

However, caution is needed, as rare adverse events such as new inflammatory lesions have been reported. A recent clinical trial comparing infliximab and cyclophosphamide shows complete neurological response rates of 71% and 57%, respectively, after 22 weeks and an adverse event rate of 30% versus 64% .

Dr Kidd then returned to speak about unmet needs in neuro-Behçet's. Problems for patients include lack of access, diagnostic delays, lack of knowledge of Behçet's among neurologists, delays in referral and treatment, and access to rehabilitation. Problems for neurologists include the complexity of neuro-Behçet's and its rapid worsening, lack of experience, and the difficulty of transferring patients to a regional or national centre. Potential solutions include formal training in systemic inflammatory diseases, active development of multidisciplinary teams and formation of networks of neurologists working in rare inflammatory diseases for diagnosis, research, data sharing and teaching.

The session finished with oral presentations of five abstracts. A presentation from the UK reported on the neurological presentations to the national neuro-Behçet's clinic at Aintree. Among 24 patients referred to the clinic, four fulfilled the criteria for neuro-Behçet's and 20 presented with headache; 18 had chronic migraine, which is a common problem and not necessarily related to neuro-Behçet's. A group from Morocco studied neuro-Behçet's in its parenchymal form, finding that 15% presented with motor deficits, 49% had cerebellar involvement and 31% had psychiatric disorders. A Russian study found that factors associated with cognitive disorders in Behçet's included age, male sex, stress, anxiety, depression, non-adherence to treatment, high disease activity and high cholesterol, but not severity or duration of Behçet's. A team from Türkiye used OCT to show that subclinical eye involvement may be more common in neuro-Behçet's than in Behçet's overall. Finally, another Turkish study showed that intracranial vessel wall imaging is a useful non-invasive technique for assessing arterial involvement in neuro-Behçet's.

Special lecture – From Behçet's disease to canker sores: the genetic architecture of autoinflammation

Daniel Kastner (USA) explained that lessons have been learned from monogenic autoinflammatory and autoimmune diseases such as familial Mediterranean fever (FMF), which was first identified in 1978. Mapping of DNA polymorphisms to chromosomes followed, with the gene for FMF being located on chromosome 16. The monogenic autoinflammatory and autoimmune diseases have defined key molecules in the innate and adaptive immune systems, respectively, while variants in certain genes, such as TNFAIP3 (codes for the A20, which regulates NF-kB), may predispose to either autoinflammation or autoimmunity, or both. Innate or adaptive immune variants that are protective against microbial pathogens may undergo natural selection in human populations. Genotype-first approaches (as opposed to phenotype first) may provide the basis for molecular diagnoses that cut across existing clinical diagnoses. However, for common diseases, it is not single genes with a large effect that are important, but common variants in several genes. Genome-wide association studies show that In the case of Behçet's, HLA-B51 is the most important gene, but many others are implicated such as ERAP1, IL-10, IL-23R, TLR4, NOD2, STAT4 and KLRC4. Both the innate and adaptive immune systems contribute to susceptibility to Behçet's. The epistatic interaction of HLA-B51 and ERAP1 strongly suggests an important role for an environmental antigen.

Scientific Session 5: Vascular Behçet's

Giacomo Emmi (Italy) began this session with a presentation on the clinical vascular phenotype. Behçet's is classified as a systemic vasculitis; it involves small, medium and large vessels, especially veins. Half of people with Behçet's have at least one vascular event, with most experiencing their first vascular event within the first 5 years after disease onset. Vascular Behçet's is more frequent and runs a more severe course in younger people, particularly males. It may develop before or simultaneously with the characteristic skin-mucosa lesions in a third of patients. The vascular disease course is almost always relapsing, with relapses at the primary site or elsewhere. The prevalence of venous thrombosis in Behçet's ranges from 14% to 40%, with deep vein thrombosis (DVT) being the main vascular involvement (75%). Superficial vein thrombosis is a characteristic feature of Behçet's and should be considered a risk factor for future vascular events. Venous thrombosis can occur at atypical sites such as the superior and inferior vena cava. Arterial involvement is less common but is associated with poor long-term outcomes; the abdominal aorta is the most common site. Coexistence of venous and arterial thrombosis is quite rare. Up to 20% of paediatric patients have vascular involvement (70% of them boys), with recurrence occurring in around 20% of those affected. Increased thickness of the common femoral vein is a distinct characteristic of vascular Behçet's.

Next, Gülen Hatemi (Türkiye) gave a presentation on the treatment of vascular Behçet's. In the case of arterial involvement, the aims of treatment are prevention of mortality, complete disappearance of aneurysms and prevention of pulmonary hypertension due to residual pulmonary artery thrombosis. For venous involvement, the aims are to prevent mortality and organ damage, prevent recurrences of venous thrombosis and prevent post-thrombotic syndrome. Many patients with vascular Behçet's respond well to immunosuppressant drugs. However, adding adalimumab to DMARD treatment led to a response rate of 34/35 compared with 23/35 for DMARD alone; the time to response was also shorter. Unlike immunosuppressants, anticoagulants do not reduce the risk of relapse of DVT or the frequency of post-thrombotic syndrome; they are also associated with a risk of bleeding. Anticoagulants may have a role in certain Behçet's patients, but a randomised controlled trial (RCT) is needed to clarify this. TNF inhibitors have also been shown to be effective in arterial disease. In one study, infliximab achieved remission in 84% of patients with pulmonary artery involvement at 6 months and 57% at 12 months, with a relapse rate during treatment of 16%. Most (62%) patients continued infliximab treatment, although some discontinued due to adverse events. In a study comparing infliximab and cyclophosphamide, vascular complete response was seen in 94% and 56%, respectively. There is a small amount of evidence of a good response to tocilizumab in patients with vascular Behçet's, and results with the JAK inhibitors tofacitinib and baricitinib are promising. Endarterectomy may have a role in some patients, such as those with life-threatening pulmonary artery thrombosis and pulmonary hypertension despite adequate immunosuppressives.

Emire Seyahi (Türkiye) then spoke about pulmonary and cardiac Behçet's. Pulmonary artery involvement is seen in 2–3% of people with Behçet's and around 10% of those with vascular involvement. It has a male predominance of six- to sevenfold and is often associated with DVT. Pulmonary artery involvement is typically bilateral with multiple lesions. Pulmonary artery aneurysms (PAAs) are a rare but serious complication of Behçet's; they are also seen in Hughes–

Stovin syndrome, which may represent an 'incomplete' form of Behçet's with vascular manifestations developing independently from mucosal lesions. Aneurysms can transform to 'giant' aneurysms with a high risk of rupture, but they can also disappear with immunosuppressant treatment. Recurrence of pulmonary artery involvement occurs in around 20% of patients; the mortality rate of around 25% has improved to 12% in recent years with earlier diagnosis and biologic therapy. The clinical phenotype is also changing, with pulmonary artery thrombosis (PAT) becoming more common than PAA. The overall prevalence of cardiac involvement in Behçet's is around 5%, with a male predominance and a mortality rate of 15–20%. All three layers (pericardium, endocardium and myocardium) can be affected, as well as the coronary vessels. The most common lesion is pericarditis (39%), followed by valvular lesions (27%), intracardiac thrombosis (19%) and myocardial infarction (17%). The prognosis is poor, but treatment with oral anticoagulants, immunosuppression and colchicine improves outcomes. Intracardiac thrombosis affects young males and may be the initial Behçet's finding. The most common cardiac valve lesion is aortic insufficiency, especially in the Far East. Coronary artery involvement also affects mainly young males, who usually have a low prevalence of traditional cardiovascular risk factors. A study in Taiwan found that the risk of ischaemic heart disease (IHD) was similar between Behçet's patients and healthy controls, although the mortality risk was higher in Behçet's; other studies have found an increased risk of IHD in Behçet's.

The next presentation, by Haner Direskeneli (Türkiye), considered controversial issues in the assessment of asymptomatic vascular disease in Behçet's with imaging. While screening of Behçet's patients for ocular involvement is routine, vascular screening during diagnosis or follow-up of patients without any vascular involvement is not feasible. However, it could be beneficial in young male patients with a severe mucocutaneous disease course. Vascular Behçet's is slowly progressive after the first attack, and while asymptomatic DVT is rare, venous insufficiency is more common. Pulmonary artery involvement can be detected early by computed tomography (CT) imaging. In a Turkish cohort of 110 patients with pulmonary artery involvement, a third of patients were asymptomatic; recurrence rates were significantly higher in symptomatic patients. An expert approach would recommend abdominal Doppler ultrasound/CT-angiography and pulmonary CT-angiography in any patient with DVT or cerebral venous thrombosis to detect Budd–Chiari syndrome, venous insufficiency and pulmonary thrombosis.

Oral presentations of four abstracts (all from Türkiye) completed the session. A systematic literature review including 261 studies on pulmonary involvement in Behçet's found that 86% of patients were male and haemoptysis (coughing up blood) was the most common symptom (74%). PAA was the most common type of involvement (39%), followed by PAT (27%), and 28% had both; the frequency of the former has been decreasing since 2000, while the latter has been increasing steadily since 1980. Mortality rates have decreased since 2000 with increased use of immunosuppressive drugs. A study of the diagnostic value of femoral vein wall thickness found that, although it was higher in Behçet's patients than in healthy controls, it could not distinguish between Behçet's and non-Behçet's patients referred to the clinic with suspected Behçet's. Another group found that 20% of their Behçet's patients with vascular involvement had stasis ulcers (venous leg ulcers); the recurrence rate was 54% and the average time to healing was 8 months. The final presentation reported on the use of direct oral anticoagulants in addition to immunosuppressive treatment in 39 patients with vascular Behçet's. No major bleeding was seen, and no patients developed pulmonary aneurysms; the relapse rate was 10%.

Scientific Session 6: Mucocutaneous Behçet's

This session began with a presentation on skin lesions in Behçet's by Christos Zouboulis (Germany). Mucocutaneous lesions are the defining characteristic of Behçet's, and around 80% of patients have skin lesions such as erythema nodosum or folliculitis/pustules. Circulating antibodies against a specific endothelial antigen activate the vascular endothelial cells to produce pro-inflammatory cytokines such as TNF and IL-8. Skin lesions such as pyoderma gangrenosum are not easy to diagnose, but thrombophlebitis is very characteristic of Behçet's. Oral ulcers are almost always the first symptom of Behçet's, but diagnosis can be delayed for years without any other symptoms. The median time from onset of the first symptom to diagnosis in the German registry is 36 months for oral ulcers, 25 months for genital ulcers, 19–20 months for erythema nodosum-like lesions or folliculitis/pustules, and 13 months for thrombophlebitis. HLA-B51 positivity is a negative prognostic factor in patients with initial mucocutaneous manifestations. Standard treatment for mucocutaneous lesions is topical or low-dose oral corticosteroid, followed by colchicine. The next line of treatment includes apremilast, azathioprine, ant-TNF agents and thalidomide. In multi-refractory disease, options include ustekinumab, secukinumab, IL-1 inhibitors and cyclosporine.

In her talk on oral health in Behçet's, Farida Fortune (UK) emphasised that oral health is associated with lifelong health. It directly affects the microbiome, which governs immune responses and the clinical outcome of diseases such as Behçet's. Throughout life, environmental and socioeconomic factors have a direct impact on Behçet's. The oral microbiome is an important link between oral and general health and is heavily implicated in Behçet's. Oral ulcers are often triggered by changes in the microbiome, leading to immune dysregulation. The salivary microbiome in people with Behçet's has increased *Haemophilus parainfluenzae* and decreased *Alloprevotella rava* bacteria; this pattern stabilises after dental and periodontal treatment. Active oral ulcers are highly colonised with *Streptococcus salivarius* and *Streptococcus sanguinus*, while non-ulcer areas have increased colonisation with *Rothia denticariosa*. Poor oral health is a predictive factor for overall Behçet's disease activity, highlighting the need for periodontal interventions as part of management. Poor oral health is a particular burden in older adults and in socially and economically deprived populations. Oral ulcers are also triggered by mechanical trauma due to ill-fitting or sharp-edged dentures, tooth fillings, fractured teeth and orthodontic braces. Preservation of natural dentition and regular dental check-ups are important in maintaining oral health. Topical mouthwashes are effective for treating oral ulcers and are cost-effective. TNF inhibitors and apremilast are effective for refractory ulcers; the former have broader benefits for other manifestations, and the latter has a corticosteroid-sparing effect in patients with milder disease. Future strategies for oral health in Behçet's should include patient empowerment to improve oral health.

Next, Jae Hee Cheon (Korea) discussed the diagnosis and treatment of gastrointestinal manifestations of Behçet's. The prevalence of gastrointestinal involvement in Behçet's shows wide geographical differences, varying between 3% and 25% and being most common in East Asia. However, intestinal Behçet's manifestations have been decreasing over time in both Japan and Korea. Genetic research in Turkish and Korean patients found a new association of intestinal (but not non-intestinal) Behçet's with HLA-B46. Typical findings in intestinal Behçet's include single or a few (<5) large ulcers in the ileocaecal area, a round or oval shape, deep ulcerations, discrete and elevated

borders, and ulcer base covered with exudates. Intestinal Behçet's can be difficult to distinguish from IBD. The clinical course of intestinal Behçet's varies; a substantial proportion of patients go into remission or have mild clinical activity, while some patients have a severe, debilitating clinical course. High disease activity at diagnosis is a negative prognostic predictor, as are older age at diagnosis and multiple intestinal ulcers. In a Korean cohort of patients with intestinal Behçet's, a quarter of patients needed surgical resection, with 5% needing more than one resection.

Khadija Echchilali (Morocco) then considered what is and what is not Behçet's in relation to musculoskeletal disorders. Musculoskeletal disorders are typical and common in Behçet's, being the third most common manifestation. Joint involvement occurs in half of all patients and is more common in males than in females; it is the first symptom in around 20% of patients. Articular Behçet's overlaps with the spondyloarthropathy (SpA) complex due to the presence of sacroiliitis in Behçet's and the clinical overlap between Behçet's and some diseases of the SpA complex. Joint involvement is the most common rheumatological finding in Behçet's, with arthritis/arthralgia affecting knee, wrist, ankle, elbow, hand and feet joints, as well as the sacroiliac joint. Enthesopathy and muscle involvement (e.g., myalgia) are less common. The inflammatory arthralgia seen in Behçet's is acute and recurrent but non-erosive and non-deforming. However, the pain and functional impairment can sometimes resemble those seen in RA and can affect quality of life. Immunological markers and X-rays are often normal, while ultrasound and MRI scans may show early signs of inflamed joints but no specific signs, making diagnosis difficult. Phenotypically, the articular cluster of Behçet's overlaps with the mucocutaneous cluster. Behçet's and SpA share many extra-articular manifestations (such as oral and genital ulcers, erythema nodosum, uveitis and thrombosis), leading to suggestions that Behçet's may be a subgroup of SpA. However, the patterns of joint involvement are different; that in SpA is erosive and involves mainly small joints. Other musculoskeletal disorders in Behçet's include pseudogout, osteoporosis, myalgia and fibromyalgia. Colchicine and azathioprine are the gold standard treatment for articular Behçet's, and the use of more aggressive treatment such as biologics remains exceptional.

Session 6 finished with oral presentations of five abstracts, the first three of which were from Türkiye. The first speaker presented a skin pathergy test with increased sensitivity that could be a promising tool for diagnosis of Behçet's, while the second showed differences in the skin microbiome between pathergy-positive and pathergy-negative Behçet's patients. Another group reported that the frequency of axial SpA in Behçet's patients with gastrointestinal involvement was no different from that in those without major organ involvement; however, although higher than in the general population, it was lower than in patients with IBD, suggesting a difference in pathogenetic mechanisms between gastrointestinal Behçet's and IBD despite the clinical similarities. The last two presentations were from the UK. The first reported the use of saliva proteome analysis to identify proteins uniquely correlated with Behçet's, while the second showed that Behçet's patients with active oral ulcers have high levels of salivary acidic glycoproteins that may be important in maintenance of oral and general health.

Scientific Session 7: Diagnosis and outcomes in Behçet's

The final session of Day 2 began with a presentation on the development of outcome measures in Behçet's by Yusuf Yazici (USA). Outcome measures are important in both clinical trials and routine

care. This is complicated in Behçet's, as different drugs have different effects in different organs. In clinical trials, outcome measures are used for the approval of new drugs or of existing drugs for new indications; they allow trial populations to be enriched with patients most likely to benefit and enable comparison of clinical trial results in meta-analyses. In clinical care, outcome measures help with making treatment decisions and evaluating response to treatment. Many outcome measures are available for assessing Behçet's disease activity, and OMERACT has developed a core set of measures for use in clinical trials in Behçet's. However, standardisation is difficult and the number of measures used needs to be reduced to allow easier comparison between trials. Outcome measures are available for disease activity, function and quality of life, as well as organ-specific measures. The lack of positive results in some clinical trials may be partly attributed to problems with study design and selection of outcome measures. Simple, clinically relevant outcome measures are needed in clinical trials to answer the research question. In clinical care, some measures should be collected in all patients, with patient-reported outcomes having an important role. The emphasis should be on better use of existing measures rather than development of new ones.

Fatma Alibaz Oner (Türkiye) then discussed classification versus diagnostic criteria in Behçet's. As Behçet's is a multisystem disorder with no gold standard test for diagnosis, criteria are needed for diagnosis and classification. Diagnostic criteria for use in routine care with individual patients need to be broad, to reflect the different aspects of the disease and to identify everyone with the disease; this requires high sensitivity with acceptable specificity. Classification criteria are used to create well-defined, relatively homogenous cohorts for clinical research, so specificity is more important than sensitivity. In an ideal world, if criteria were 100% sensitive and 100% specific, the same criteria could be used for both purposes. It is difficult to capture all disease presentations in a single set of criteria, and the performance of any criteria depends on the prevalence of the disease in a geographical area. The current criteria for Behçet's have several limitations. The International Study Group (ISG) criteria were created using a population mainly from the Middle East where gastrointestinal involvement is rare; they do not include other major organ involvement such as vascular and neurological. The International Criteria for Behçet's Disease (ICBD) have better sensitivity and worse specificity than the ISG criteria; this can lead to over-diagnosis in areas with low prevalence (most of the world). Revised criteria proposed by the Behçet's Disease Research Committee of Japan include incomplete and possible diagnosis of Behçet's as well as definite diagnosis; they may be more useful in countries with low prevalence. In practice, Behçet's is still mainly a clinical diagnosis depending on exclusion of other possible diagnoses. One way forward in high prevalence areas might be to define a group of people at risk for developing Behçet's (e.g., recurrent oral ulcers, family history of Behçet's, HLA-B51 positivity). As presentation with limited disease manifestations (especially with major organ involvement) is increasing, organ-based diagnostic criteria may also be needed.

A presentation by Isabel Koné-Paut (France) looked at the diagnosis and classification of paediatric Behçet's. Challenges for the diagnosis of Behçet's in children include its rarity, the small number of symptoms/signs, the long delay from first symptom to completion, monogenic mimics that need to be excluded and the clinical heterogeneity. The paediatric criteria published in 2016 require three of six items for classification as Behçet's (recurrent oral ulcers, genital ulcers, skin involvement, ocular involvement, neurological signs and vascular signs). Validation of these criteria showed very high specificity (99%) but low sensitivity (58%). Clinical characteristics of paediatric Behçet's vary geographically; for example, both neurological and gastrointestinal involvement are higher in Europe than in Türkiye or Iran, while vascular involvement is higher in Türkiye. A positive family history and

atypical features such as fever, deep ulceration or severe colitis may suggest a genetic cause such as A20 haploinsufficiency or mevalonate kinase deficiency.

Gülen Hatemi (Türkiye) then considered whether the objective of treatment to target in Behçet's is realistic. Many different drugs are used to treat Behçet's, but it is not treated optimally as 80% of patients still experience accumulation of damage. A treat-to-target strategy defines a treatment target and applies tight control (e.g., monthly visits and therapy adjustment) to reach that target. The strategy often follows a protocol for treatment adjustments based on disease activity and response to treatment. Such strategies are commonly used in diabetes and hypertension. Considerations include whether targets exist that would predict achievement of the desired long-term outcome, what degree of toxicity and cost would be acceptable to achieve the outcome, and how often the patient needs to be monitored. The European Alliance of Associations for Rheumatology (EULAR) has made recommendations for treating to target in RA, and the strategy has been shown to improve outcomes; however, good outcome measures are available for RA. In a symposium, experts were asked to suggest long-term goals and short-term treatment targets for various Behçet's manifestations, as well as how (and how often) to monitor patients. For example, the long-term goal in eye disease would be preserving vision, while the short-term target could be angiographic remission monitored with fluorescein angiography every 3–6 months initially and then every 6–12 months. The treat-to-target strategy developed for IBD could be adapted for gastrointestinal Behçet's. Challenges in developing a treat-to-target strategy for Behçet's include the need to assess each involved organ; a composite index such as the Behçet's Disease Clinical Activity Index (BDCAI) is useful in practice but is not ideal as a treatment target. An ideal target should predict long-term damage and function reliably and should be feasible in terms of cost and time required. To develop a treat-to-target strategy for Behçet's, suitable treatment targets need to be identified and trials need to be designed to show that treating to these targets improves long-term outcomes.

The day finished with oral presentation of five abstracts, three of them from Türkiye. The first presented the results of prospective follow-up of an inception cohort of 55 patients with suspected/incomplete Behçet's. Most patients presenting with limited clinical findings started with major organ involvement; a third of patients experienced relapse or new organ involvement over 48 months. Another group reported prospective follow-up of 36 young male patients with major organ involvement, 13 of whom needed immunosuppressive therapy; 8/13 needed step-up treatment due to relapse or a new major event. The third presentation reported on a systematic review of outcome measures used to assess OMERACT (Outcome Measures in Rheumatoid Arthritis Clinical Trials) core domains for clinical trials in Behçet's, highlighting the diversity and variability of instruments used and the lack of disease-specific tools for most types of organ involvement. The first of two presentations from Morocco described the identification of clinical clusters in a large cohort of Behçet's patients. Five distinct clinical profiles were identified, with different gender profiles and management (neurological, oculo-vascular, cardio-vascular, ocular, skin-mucosa + articular). Finally, a study in 38 children with Behçet's found that 55% met the 2016 paediatric Behçet's criteria while 68% met the 2014 ICBD criteria and 37% met the 1990 ISG criteria.

Special lecture – Behçet's disease in 2030

Ahmet Gül (Türkiye) began by summarising the timeline of Behçet's research from the first case series in 1937 through the discovery of the link to HLA-B52 in 1973, the development of immunosuppressants in the 1980s and 90s, and the first use of infliximab in 2001 to the recognition of the role of the microbiome in 2015. Regarding pathogenesis, we can expect more detailed genetic/genomic and immunological analyses with larger sample sizes and broader coverage of the variants, as well as greater knowledge of the role of the microbiome and environmental factors, possibly leading to dietary interventions and therapy with probiotics and metabolites. In the area of disease/phenotype definitions, there may be progress towards a new taxonomy based on genotypes and recognition of disorders with overlapping manifestations and treatment targets. As regards diagnosis and monitoring, manifestation-specific criteria may be developed and a new taxonomy could unlock a potential diagnostic role of genetic risk scores. Education for physicians and patients should continue to improve; Behçet's is a rare disease with important impacts on the differential diagnosis of other diseases. Available treatments should be used in a more targeted and personalised way, supported by study of larger cohorts with more detailed genetic analysis and identification of disease-specific inflammatory pathways. From the patients' perspective, these advances should lead to earlier diagnosis and more effective treatment of the manifestations of Behçet's and the possibility of induction of long-term remission (or even cure). Patients all over the world should be able to expect easy access to reference centres and effective treatments. Preventive measures will include education, better oral and general hygiene, changes in diet and other modifiable environmental factors, and screening of family members.

Scientific Session 8: Old drugs/new drugs in Behçet's

In his presentation looking at whether there is still a place for immunosuppressants in Behçet's, Yusuf Yazici (USA) stated that in fact they should be used more than they currently are. It is unlikely that a single drug will work for all Behçet's manifestations, and many patients will need a combination of an immunosuppressant and a biologic agent. Treatments recommended by EULAR for mucocutaneous involvement include colchicine, apremilast, azathioprine, thalidomide, interferon-α and anti-TNFs. Colchicine is safe and can achieve a rapid response in some patients, so it is worth trying. Apremilast can be added in case of an insufficient response and then tapered. For ocular Behçet's, EULAR recommends azathioprine, anti-TNFs, cyclosporine and interferon-α, but questions remain about the relative efficacy of azathrioprine and TNF inhibitors, whether they should be used in combination and when they should tapered or stopped. One approach may be to start with azathioprine and add an anti-TNF if needed, while an alternative is to start with the combination and then taper the TNF inhibitor. For vascular involvement, DMARDs plus adalimumab has been shown to be superior to DMARDs alone in resolving venous thrombosis, but it is not known whether the benefit is due to the combination. EULAR recommends azathioprine, TNF inhibitors and cyclophosphamide for neurological involvement; infliximab may be more effective than cyclophosphamide, but data on infliximab versus azathioprine is lacking. For gastrointestinal Behçet's, EULAR recommends 5-aminosalicylic acid, azathioprine, anti-TNF and thalidomide. It may be that starting with a combination is the best option; around 15% of patients on TNF inhibitors develop new manifestations, so combination with a DMARD may be needed for total control.

Next, Petros Sfikakis (Greece) discussed whether anti-TNF agents are the 'new corticosteroids' in Behçet's, starting by saying that corticosteroids have never been a panacea and neither are TNF inhibitors. TNF inhibitors are no longer new in the treatment of Behçet's; they have high efficacy across all clinical domains, but the timing of their introduction and the duration of treatment are still open to question, as is whether they should be used alone or in combination with a DMARD. In 2019, an RCT in 555 Japanese patients with Behçet's uveitis showed an 81% response rate with infliximab, while a study in Spain suggested that adalimumab may be better than infliximab in terms of long-term outcomes. A meta-analysis including 1156 patients found an 85% remission rate for ocular inflammation with TNF inhibitors. Infliximab monotherapy has been shown to be non-inferior to combination therapy over 10 years of follow-up. Overall, earlier use of TNF inhibitors in ocular Behçet's leads to better long-term outcomes. For venous thrombosis, the time to response has been shown to be shorter with DMARD plus adalimumab than with DMARD alone. A recent RCT showed that induction therapy with infliximab led to a 94% complete response rate in vascular Behçet's compared with 56% for cyclophosphamide; the complete response rates for neuro-Behçet's were 71% and 57%, respectively. A meta-analysis reported a 94% response rate with infliximab in neuro-Behçet's, with earlier treatment giving better results. A meta-analysis in gastrointestinal Behçet's also showed good rates of clinical remission and mucosal healing. Among 282 Behçet's patients treated with infliximab, the most common indications were uveitis (n=137) and vascular involvement (n=91), and only 19 (7%) experienced new manifestations. There are now >900 publications on the use of TNF inhibitors in Behçet's, and it would seem reasonable to propose that over the next 5–10 years, all patients with ocular, vascular, neurological or gastrointestinal involvement should receive a TNF inhibitor as first-line treatment (unless contraindicated), with a treatment target of disease remission and consideration of discontinuation after 2 years' remission. Patients refractory to TNF inhibitors should be conserved 'difficult to treat' and should receive another biologic agent.

Jacob Van Laar (Netherlands) then considered interleukins and anti-interleukins in Behçet's, saying that he was lucky to be practising in a country where these drugs are available. The therapeutic rationale for using these agents in Behçet's is that multiple pro-inflammatory interleukins (including IL-1, IL-2, IL-6, IL-10 IL-12, IL-13, IL-17 and IL-22) are produced by the pathogenic pathways involved in Behçet's. New treatment options in Behçet's include: the anti-IL-1B agents anakinra, canakinumab and gevokinumab, which are used for uveitis and mucocutaneous involvement; tocilizumab, an anti-IL-6 agent that is effective in uveitis and possibly in neuro-Behçet's; and the anti-IL-12/IL-23 agent ustekinumab and anti-IL-17 agent secukinumab used for mucocutaneous manifestations. Much of the data on these agents comes from observational, often retrospective, studies in small numbers of patients, with little positive evidence from RCTs. The side effect profiles of these agents seem to be acceptable, although less good than TNF inhibitors.

Oral presentations of four abstracts concluded the scientific programme. The first reported that despite not being included in the latest EULAR recommendations, methotrexate is still widely used in Behçet's in Spain, often in combination with a TNF inhibitor; as monotherapy, it was most effective in the articular phenoptype. A group from the UK examined medication adherence in Behçet's, finding that around a third of patients missed doses at least a few times a month; they concluded that an individualised approach encompassing patient support, education and implementation of tailored treatment plans can improve compliance and ultimately patient outcomes. A study from Türkiye assessed the frequency of de novo manifestations of Behçet's during adalimumab treatment. Among 335 patients, 14 patients (4%) experienced de novo manifestations, of which 5 (36%) consisted of

vascular involvement; this low frequency may suggest that TNF inhibitors modify the disease course of Behçet's. Finally, researchers from Greece reported that drug-free remission of >5 years (up to 20 years) after withdrawal of anti-TNF therapy occurred in 50% of patients with previously severe Behçet's; they suggested that discontinuation of TNF inhibitors should be considered in all patients treated successfully for 2 years.

Closing remarks

The conference finished with the presentation of several poster prizes. It was announced that the 21st ICBD will take place in Turkey in 2026.

Clare Griffith