2019 Conference and AGM

The 2019 Conference and Annual General Meeting took place at Pavilions of Harrogate on Saturday 19 October and was attended by more than 80 people.

AGM business

Welcome and report from the Chair

Tony Thornburn welcomed everybody to the AGM, passing on apologies from Professors Robert Moots (Liverpool) and Farida Fortune (London) who were unable to attend. Tony introduced the Society's trustees, adding that additional trustees were always welcome; there is currently no trustee from Northern Ireland. He also introduced the administrators, saying what a great job they do.

Tony reminded members of the aims he had outlined at the previous two AGMs, the first of which was clarity of purpose and coherence. To this end, the renaming and rebranding of the Society was achieved relatively cheaply and had been very successful. In addition, the website has been improved, social media presence has increased and factsheets have been updated, with new factsheets on ulcers and psychological aspects of Behçet's being added. Another aim was to increase the visibility of Behçet's, which had been achieved by membership of more organisations and by political lobbying. More interactive communication with members remains a vital goal, and processes for the Helpline are being refined to meet members' needs.

Tony thanked the people who have organised support groups around the UK, and all the members and supporters who have been involved in fundraising.

The final aim was a focused and targeted research effort, and the first research award has been established with the Royal Society of General Practitioners. In addition, a NICE-accredited guideline for Behçet's is being developed by the British Society for Rheumatology and the British Association of Dermatologists. A workshop at the EURORDIS Annual Meeting identified trends such as the increasing importance of data capture and interpretation, and the rise of genomics and personalised medicine. A survey had found that people with rare diseases were much more willing than others to share their data (97% versus 37% of the general public), particularly with medical doctors and researchers from non-profit organisations. Tony said that patients need to have control over the management of and access to their data, aligned with robust standards that are secure, ethical and responsible. Plans are being developed for a UK-wide Behçet's Patient Registry. Other research efforts include a multicentre retrospective observational study on the prevalence and incidence of Behçet's in England, a research initiative in Northern Ireland and the Behçet's UK/BPC Quality of Life Survey to be conducted in January 2020.

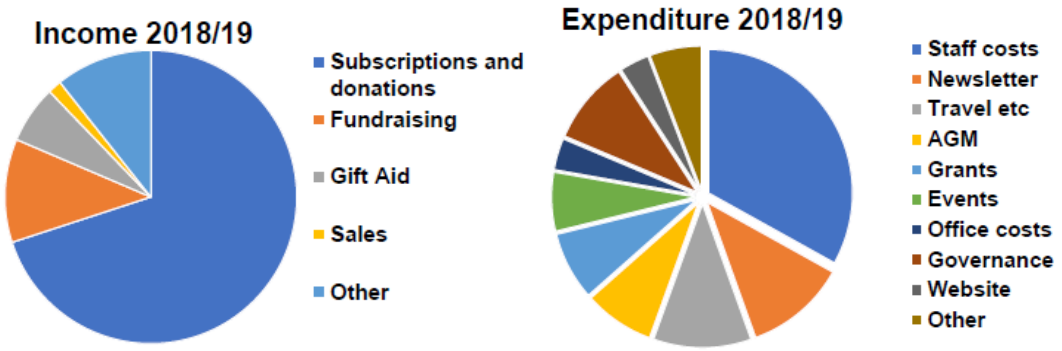
Tony finished by saying that the Society is fundamentally reliant on the engagement of its membership and encouraged members to respond to requests for information and opinions. He highlighted the need for the Society to find new income streams and to identify a president and patrons.

Financial report

Alan Lane reported that the Society has 1058 full members, with 14 junior members, 77 associates, 32 donors and 55 possibly lapsed members. This represents a continuation of the steady increase seen in recent years. The proportion of members in receipt of benefits or pensions has also increased, now standing at 79%, meaning that income from subscriptions has decreased. Almost three-quarters (73%) of members are women, and 55% are aged 55 or older.

The largest part of the Society's income comes from subscriptions and donations, followed by fundraising and Gift Aid. Sales of merchandise were low in the past year

due to the rebranding, but a good new range should see sales increase. Staff costs represent the largest proportion of expenditure (about a third), with governance, travel and the newsletter making up another third. A lot of the governance expense was due to legal disputes over a large legacy, which could be the Society's largest ever donation. For 2018/19, the Society's total income was £43,319 and the total expenditure was £73,367. Compared with the previous year, the expenditure has increased more than the income, and the balance is now down to the minimum desirable level (~£30,000). However, Alan pointed out that charities have a duty to spend money rather than save it. The Research Fund has a balance of £15,000.



Alan listed the ways that members and supporters can help as joining the Society, making a donation, buying merchandise, shopping through Amazon Smile, fundraising through events and on Facebook, donating through sales on eBay, playing the Weather Lottery, recycling ink cartridges and considering making a bequest.

News from the Society

Judi Scott confirmed that the annual subscription remains at £20 for 2019/20, while the limit for grant aid has increased to £1000. Grants are made to improve people's quality of life, and anyone can apply once they have been a member for 6 months. Judi also highlighted the amount of work that goes into the quarterly newsletter and encouraged people to send items for inclusion. Gemma Darlow mentioned some of the amazing fundraising efforts throughout the year, and reported that the 2019 Family Day had been a great success.

The Judith Buckle Award

Richard West reminded the audience that Judith Buckle had started the Behçet's Syndrome Society in York in 1983, and it had grown from very small beginnings to today's Behçet's UK with more than 1000 members. This year's recipient of the Judith Buckle Award was Dr Edmund Jessop, a health service manager who had encouraged and supported the Society in setting up the three Centres of Excellence. Dr Jessop played a very important role in advising on the National Commissioning process, and his guidance had been invaluable. Richard presented the award to Jan Mather, who received it on Dr Jessop's behalf. In a video, Dr Jessop said that the award was a tremendous honour and that he had found the process of established the Behçet's centres very rewarding and was delighted that the process had gone so well.

Concepts and challenges in Behçet's – a clinician's view

Dr Deva Situnayake, Clinical Lead at the Birmingham Centre, described Behçet's as a puzzle and the role of the clinician as trying to find order out of chaos. Challenges in the clinic include unravelling the problems and treating the whole person, and deciding what targets to treat to. He stressed that this involves a whole team of people, including the patient. The 'puzzle' of Behçet's includes the gender, age, ethnicity and past family and medical history of the patient. For example, ocular and vascular involvement are more common in men, while erythema nodosum and joint involvement are seen more often in women. Male patients tend to be younger, and late onset (after 40 years of age) is more common in women. Oral ulcers can precede the

diagnosis of Behçet's by many years, with the diagnosis being made only when sufficient other symptoms have appeared. Registries will enable the probabilities of different symptom combinations to be calculated and their associations to be determined.

There seem to be different subsets of Behçet's patients, which may overlap with other conditions. For example, a gastrointestinal Behçet's phenotype has similarities to inflammatory bowel disease (IBD); distinguishing Behçet's and Crohn's disease endoscopically can sometimes be difficult, and there may be similarities in the biological basis of the two conditions. Similarly, neuro-Behçet's may resemble multiple sclerosis and a arthritis/acne/enthesitis phenotype can be compared to seronegative spondyloarthropathy. Studies in Japan, where registries have been established for some time, have found that the prevalence of gastrointestinal Behçet's is increasing while ocular Behçet's is decreasing. Crohn's disease has also increased in Japan, which is possibly related to a more Western-style diet.

Multiple biological pathways underpin Behçet's, and the different manifestations may be related to different pathways. Biological therapies block these pathways in different places, and it may be possible to target treatment on the basis of common pathways shared by Behçet's and the conditions that overlap it. For example, the spondyloarthropathies (ankylosing spondylitis, reactive arthritis, psoriatic arthritis and arthritis associated with IBD) have a shared immunopathological basis involving barrier dysfunction and aberrant innate immune reactions at sites of mechanical stress. The cytokine IL-23 seems to be a unifying factor between spondyloarthropathies, IBD and Behçet's, offering a rationale for the use of ustekinumab, a biologic drug that is effective in psoriatic arthritis and Crohn's disease, in Behçet's patients with a gastrointestinal phenotype. Tocilizumab, which acts on IL-6, may have potential in vascular and ocular phenotypes, while secukinumab, which targets IL-17, has been reported to induce Behçet's.

However, Dr Situnayake pointed out that targeting the biology of Behçet's may not be the complete answer. Not all aspects of the disease will improve at the same rate, and not all elements will respond to immunomodulatory treatment (for example, established damage and non-inflammatory aspects of the disease such as fatigue). Ideally, personalised targets or goals for treatment are set in the clinic. A 'treat-to-

target' approach is well established in rheumatoid arthritis and is also being used in systemic lupus erythematosus. Treatment is titrated using a single disease activity measure with the aim of achieving a low disease activity state that leads to improved outcomes. However, this approach is more difficult in Behçet's, as no single measure encompasses all aspects of the disease. Integration of multiple measures may be needed, which will be facilitated by the multidisciplinary approach used at the Behçet's centres.

The epidemiology of Behçet's

Dr Priyanka Chandratre from the Birmingham Centre spoke about the project to investigate the epidemiology of Behçet's in England using data from the three centres. Over the decades since the 1970s, pooled estimates of prevalence per 100,000 population are 119 for Turkey, 31 for the Middle East, 4.5 for Asia and 3 for Europe. In England, a prevalence of 0.64 per 100,000 was reported from a small survey of Yorkshire GPs in 1977. When looking at prevalence data, it is necessary to consider the classification criteria used to diagnose Behçet's. The ICBD 2014 criteria are more sensitive but less specific than the ISG 1990 criteria; they may identify more cases, but some of them may not actually be Behçet's. In addition, studies in high prevalence areas used sample surveys, while those in low prevalence areas used census surveys, so the true geographical differences may not be as great as reported. Dr Chandratre also noted that the frequency of the HLA-B51 gene only explains moderate variations in prevalence.

Dr Chandratre explained that the planned study was needed to enable more resources for the Behçet's population, and to investigate the phenotype of Behçet's by system involvement and ethnic group. It will also enable the study of cohorts over time to see disease evolution (as has been done in Japan), and to determine whether there has been a change in outcomes since the inception of the National Behçet's Service in 2012 and access to biologic drugs. Linkage to a registry would allow more detailed investigations.

The aim of the study is to establish the prevalence of Behçet's in adults in England, and then the UK. Following establishment of the proof of concept in Birmingham, the

capabilities and referral networks of the Centres of Excellence will be utilised. There are four objectives:

1. Calculating the prevalence and incidence of Behçet's (stratified by ethnicity and gender)
2. Descriptive statistics for demographics, clinical characteristics, end organ damage, treatments and disease activity (Behçet's Disease Current Activity Form (BDCAF) score/EQ-5D visual analogue scale)
3. Regression analysis to assess association between independent variables and BDCAF/EQ-5D
4. Cluster analysis of clinical manifestations of Behçet's

UK residents aged 18 and over with a confirmed diagnosis of Behçet's will be included, using data from the Behçet's centres, the British Paediatric Surveillance Unit (BPSU) and Hospital Episode Statistics (HES). Pilot work in HES records from 2003 to 2017 has identified 4403 patients coded as having Behçet's, either as the main diagnosis for that admission or as a co-morbidity. Work will be done to cross-reference this data with clinical records in NHS trusts. The prevalence will be determined as all patients with a definite diagnosis of Behçet's seen in one of the centres, identified by the BPSU or coded by HES. The denominator will be the UK population in the years covered by the study. Incidence will be determined as new diagnoses of Behçet's made during a consultation at one of the centres or during a secondary care contact episode. A questionnaire sent to physicians will ask about demographics (age, gender and ethnicity), symptoms/disease manifestations, EQ-5D-5L, most recent treatments and the flare record (number of flares and area affected).

Pilot work at the Birmingham Centre, using the adult population of the catchment area (~16 million people) as the denominator, identified 296 patients who met the inclusion criteria between 2012 and 2108. This gives a prevalence of 1.75 per 100,000. However, the catchment population is difficult to define geographically and will overlap with the other centres. The mean age of the identified patients was 44 years, 37% were male and 67% were of white ethnicity. The most common source of referral was rheumatology (42%), followed by general practice (19%). Baseline disease characteristics are shown in the table.

Oral Ulceration	238 (80.4%)
Genital Ulceration	189 (63.9%)
Skin signs/symptoms	109 (36.8%)
Musculoskeletal signs/symptoms	43 (14.5%)
Neurological signs/symptoms	9 (3.0%)
Gastrointestinal signs/symptoms	17 (5.7%)
Vascular signs/symptoms	17 (5.7%)
Pathergy	12 (4.1%)
Ocular signs/symptoms	89 (30.1%)
Clinical end organ damage	
Ocular	151 (51.0%)
Neurological (Parenchymal)	32 (10.8%)
Neurological (Non-parenchymal)	10 (3.4%)
Major Vessel disease (Arterial)	8 (2.7%)
Major Vessel disease (Venous)	47 (15.9%)
Current treatment modality	
Steroid therapy	194 (65.5%)
DMARD therapy	129 (43.6%)
Biologic Therapy	96 (32.4%)
Transformed index score (n=179)	5 (3-8)
EQ VAS (n=48)	55 (45-75)

Dr Chandratre said that national data are needed, which would allow linkage to genetic and other studies, and could also serve as a starting point to establish a national disease registry. Tony Thornburn confirmed that the Behçet's UK Trustees have agreed to fund the study.

Neutrophils and NET production

Dr Graham Wallace of the University of Birmingham spoke about the role of neutrophils in Behçet's. Neutrophils are essential components of the innate immune response and are abundantly present in the circulatory system, comprising 50–70% of total circulating white blood cells. They are the first white blood cells to migrate from the blood to injured or infected sites to kill pathogens, resulting in swelling, redness and pain. It is hypothesised that activation of neutrophils at mucosal surfaces contributes to ocular inflammation in Behçet's.

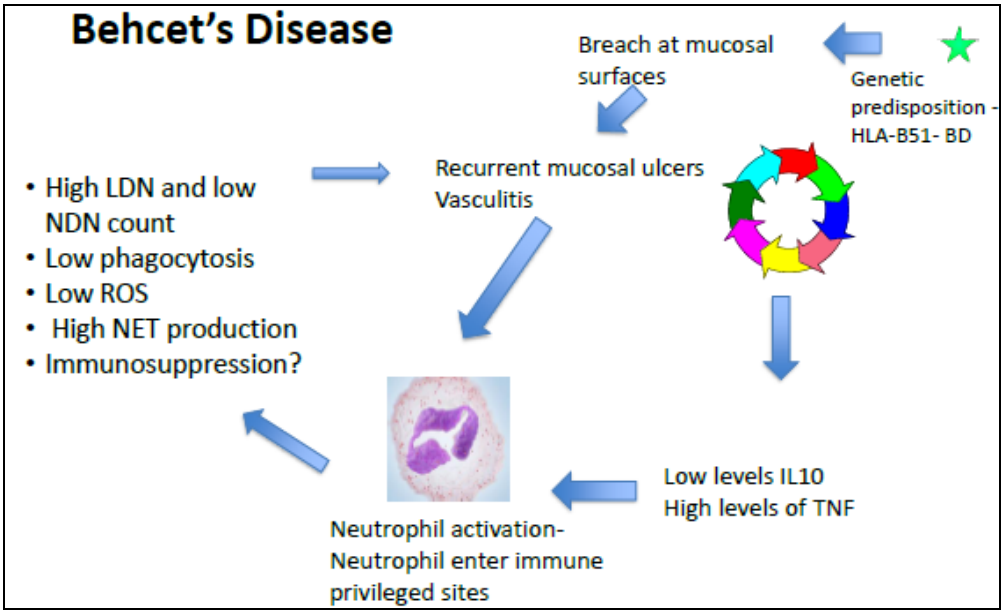
Neutrophils are phagocytic, 'eating' and destroying pathogens labelled by the attachment of antibodies, and producing reactive oxygen species (ROS). Phagocytic activity and production of ROS have been shown to be lower in neutrophils from Behçet's patients than in those from healthy controls.

Low density neutrophils (LDNs) are a subpopulation of neutrophils that are functionally and structurally different from normal density neutrophils (NDNs) and

have been found in systemic lupus erythematosus, cancer, HIV and sepsis. Compared with healthy controls, Behçet's patients were found to have more LDHs and fewer NDNs, and the phagocytic capacity and ROS production was lower in both LDNs and NDNs.

Activated neutrophils can undergo NETosis, which may be an active form of cell death and leads to the release of strands of nuclear DNA known as NETs (neutrophil extracellular traps) which trap and kill many types of microbes. Neutrophils in Behçet's patients appear to be capable of high levels of NETosis, although NET production in response to stimulation by *Escherichia coli* may be reduced. Other work has found increased NET production and increased levels of NET components in Behçet's. In addition, serum from Behçet's patients has been shown not to induce NET production, whereas serum from patients with other conditions such as Crohn's disease does.

Neutrophils carry a variety of surface markers, the expression of which has been found to differ between Behçet's patients and healthy controls. For example, CD66b and CD33 are expressed to a greater extent by both LDNs and NDNs from Behçet's patients. These may correspond to a population of immunosuppressive neutrophils. In summary, neutrophils seem to have a complex role in the pathogenesis of Behçet's.



Behçet's Patients Centres update

John Mather, BPC Operations Manager, explained that Behçet's Patients Support complements the national clinical service that NHS England commissions from the three centres in England, providing information and support to patients with Behçet's. It works in partnership with Behçet's UK, the centres and NHS England. The three Behçet's Support Coordinators support patients to stay in work or education and to stay active, helping them to live well – within the constraints of their Behçet's. The support coordinators provide benefits information, emotional support and advocacy support, acting as a bridge between doctor and patient, and between the patient and other organisations.

Behçet's Patient Support has recently undergone a rebranding exercise to promote a more patient-focused image for the support coordinators. The new logo has a modern design, and the strapline "In partnership with the NHS and Behçet's UK. Helping people with Behçet's live well" reflects the role of the support coordinators. A website with the address "www.behcetspatients.co.uk" will soon be available to provide a single source of information for the centres.

Behçet's Patients Support

John finished by saying that the Behçet's Quality of Life Survey 2020 will update the information on the impact of Behçet's on quality of life collected in the 2009 and 2014 surveys. The aim is to better understand:

- How Behçet's presents itself across patients diagnosed with the condition
- How diet affects the symptoms
- Whether the centres of excellence are meeting the medical needs of patients
- Whether the support provided by the support coordinators is meeting the non-medical needs of patients
- Whether Behçet's UK is meeting the needs of patients
- How Behçet's compares with other illnesses

Finally, the survey will provide the most robust data collected to date for Behçet's patients across the UK, which could be used as the basis for future research.

Behçet's disease: pregnancy and beyond

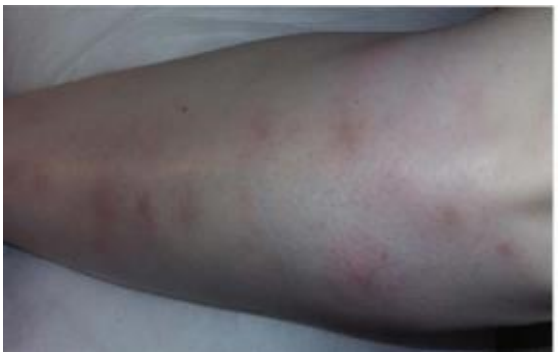
Rachael Humphreys began by pointed out that pregnancy is an important issue in Behçet's, as symptom onset often occurs during people's fertile years. Information about pregnancy, its outcome and safety is vital for patients considering starting a family. Rachael spoke about her two very different experiences with pregnancy in the past 6 years.

Rachael explained that she was diagnosed with Behçet's in 2004 when she was 24. She had very aggressive symptoms and very quickly climbed the medication ladder, with little effect on disease activity and a large impact on her quality of life. She started infliximab in 2007, which had such a great effect that she was able to train to be a paediatric nurse. The subject of starting a family often came up in her clinic appointments, and her main anxiety was how a pregnancy would be managed in the presence of Behçet's and what to expect. She was told that patients with autoimmune diseases often go into remission during and immediately after pregnancy, but that there was no way of predicting what would happen. She would just have to "wait and see".

Case series in the medical literature show varying rates of remission versus flare during pregnancy in Behçet's patients, with an overall rate of 58% remission and 30% flare. A retrospective study of 76 pregnancies in 46 women reported flares in 27 (35%) pregnancies – 19 during gestation and 18 post-partum – while 49 pregnancies were flare-free. So, while some of the data in the published work are conflicting, two conclusions can be drawn: Behçet's tends to go into remission during pregnancy, and most exacerbations occur as recurrent oral and genital ulcers. Rachael concluded that it was a gamble, but the odds were in her favour.

In her first pregnancy, in 2012/13, Rachael remained on infliximab until 23 weeks and had no Behçet's symptoms at all. She had the usual midwifery appointments, consultant-led with an added growth scan, plus one rheumatology appointment during pregnancy. The main concern was managing reflex anoxic seizures in the presence of

labour. Joseff was born at 38+3 weeks; Rachael had a flare-up of eye disease 3 days before labour, a flare-up of erythema nodosum during labour, and a flare-up of oral and genital ulcers 12 hours after the birth. By postnatal day 3, the erythema nodosum was worsening; it did not respond to 40 mg prednisolone.



Rachael re-started infliximab 5 weeks after the birth, but the eye disease and the erythema nodosum took the best part of a year to stabilise. The rheumatologist told her that if she decided to have another baby, she should have intravenous hydrocortisone during and after labour.

In Rachael's second pregnancy in 2016/17, she had a flare-up of erythema nodosum in the first 6 weeks. A change in the guidelines meant that she had to stop taking infliximab at 10 weeks, and the erythema nodosum was unresponsive to high-dose prednisolone. This time, Rachael was off work from 17 weeks and had intensive midwifery, obstetric and rheumatology input. She was started on certolizumab pegol (Cimzia) at 29 weeks, as it is the safest biologic drug in pregnancy, with injections at home continuing until 37+3 weeks. Anwen was born at 37+6 weeks, 3 days after the last dose of Cimzia. Rachael had recurrent episodes of mastitis over 10 weeks, resulting in two hospital admissions for intravenous antibiotics.

After a few detours and admissions for intravenous steroids, Rachael is now on adalimumab and is not planning any more pregnancies. She said that juggling Behçet's and being a mum is difficult. Behçet's is so unpredictable that you can never know how it will respond to pregnancy, as demonstrated by Rachael's two very different pregnancies and postnatal experiences. Anyone with Behçet's who is planning a pregnancy needs a clear plan to cover all possibilities.

Never mind the quality, feel the width: psychological aspects

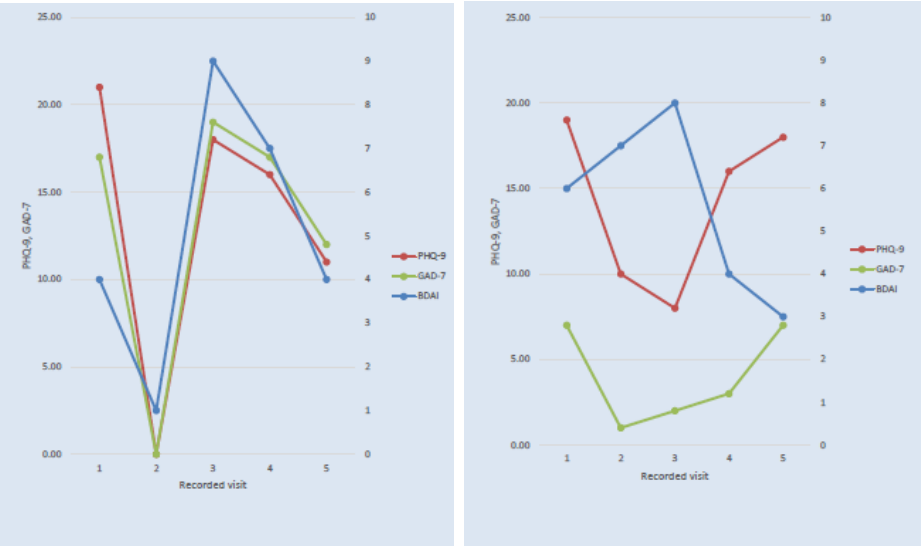
Prof Phil Murray, Consultant Ophthalmologist in Birmingham, defined quality of life as the feeling of overall life satisfaction, as determined by the mentally alert individual whose life is being evaluated. Quality of life in Behçet's is affected by characteristics of the individual (e.g. disease flares, stress, anxiety, fatigue, depression, frustration and anger) and environmental factors (e.g. relationships, education, social and leisure activities, financial situation, employment and the side effects of treatment). However, most studies of quality of life in Behçet's have been a snapshot a single time point, with little information on how it changes over time. The Centres of Excellence provide an ideal opportunity to capture longitudinal data to discover whether improvement or worsening of disease activity is mirrored by a similar change in psychological status.

Prof Murray presented results from a study that aimed to determine the relationship between disease activity and psychological status in Behçet's patients using validated health questionnaires over a 2-year period. Patients attending the Birmingham Centre between January 2016 and December 2017 who had seen a rheumatologist, ophthalmologist, oral medicine specialist and clinical psychologist at each visit on more than one occasion were included. At each visit, questionnaires were completed to assess disease activity and various aspects of quality of life and mental wellbeing. A total of 257 patients attended during the study period, and 102 fulfilled the criteria for inclusion in the study.

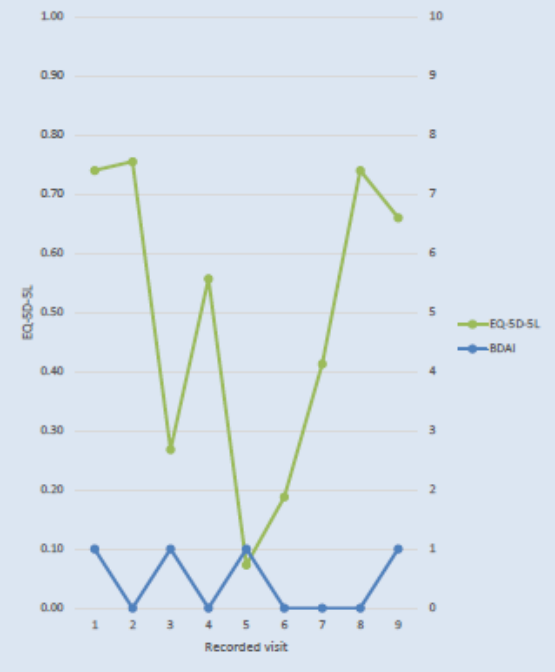
As disease activity increased, there was a slight worsening of quality of life and all the psychological questionnaires, including anxiety and depression. As the clinician's and patient's perception of disease activity improved, there was a slight increase in quality of life and wellbeing, and an improvement in depression, anxiety, and work and social adjustment. As the number of symptoms increased, the patient's and clinician's perception of the disease activity worsened. Interestingly, patients' and clinicians' perceptions were more important than disease activity in predicting anxiety and depression.

These results show the general picture over the 2 years, but individual patients showed different patterns of associations. For example, in one patient, changes in

disease activity scores were closely mirrored by changes in anxiety and depression scores. However, in another patient, anxiety and depression scores worsened after visit 3 despite an improvement in disease activity.

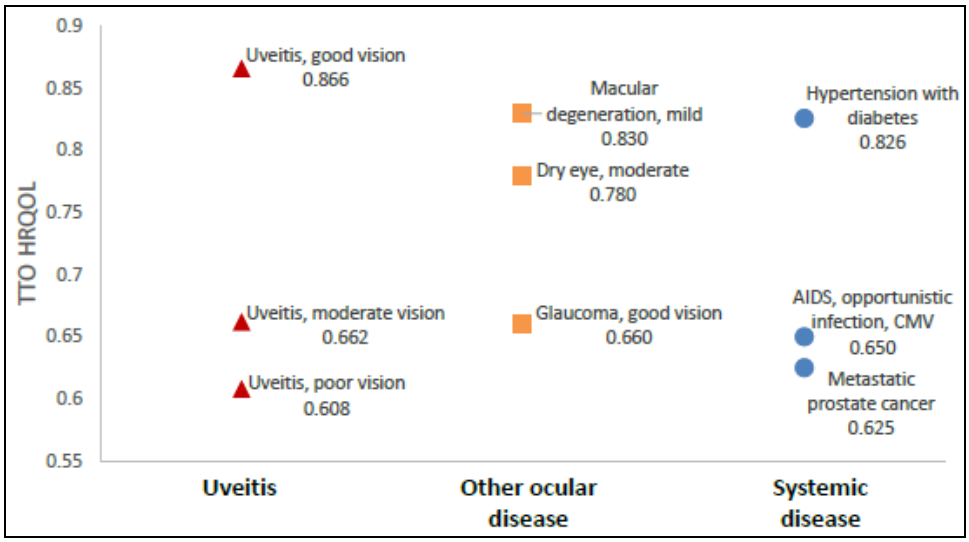


A third patient had consistently low disease activity but marked fluctuations in quality of life.



Thus, changes in disease activity account for only a small proportion of changes in psychological status. This study was published in *Ocular Immunology and Inflammation* in August 2019.

Prof Murray finished by saying that health-related quality of life direct health utilities are preference values that patients attach to their overall health status, where perfect health = 1.0 and death = 0. They can be used to compare values across different diseases. Thus, the effect of Behçet's can be compared with that of heart disease or cancer, for example. The time-trade-off (TTO) model is one way of determining health utility, asking patients what is the maximum number of years (if any) that they would be willing to trade in return for guaranteed perfect health for the rest of their life. Another is the standard gamble model, which asks about the maximum percentage risk of death (if any) that patients would be willing to accept to have perfect health for the rest of their life. Use of the TTO model in uveitis showed that uveitis with poor vision had an impact similar to that of metastatic prostate cancer. Similar research is now being done in Behçet's.



Medical Panel Q&A and Conference close

The day finished with a question and answer session with the medical speakers. The panel was asked whether Behçet's is considered an autoimmune or an autoinflammatory disease. They said that it is usually thought of as a mainly autoinflammatory disease, with a small autoimmune component; however, most treatments target downstream pathways, so the original mechanism does not affect therapy. In response to a question about the role of diet in Behçet's, Dr Wallace said that there is some evidence for certain foods triggering flares of oral ulcers. Regarding the role of the gut microbiome, no particular organism in the gut flora has been

conclusively linked to Behçet's and the link between diet and the microbiome is not very strong. Asked whether neutrophils might be useful in the diagnosis of Behçet's, Dr Wallace replied that LDNs are found in many different diseases, although the subpopulations may vary, and the normal ranges for the different cells are very wide.

Clare Griffith, Editor