Behçet's disease

Behçet's disease: global epidemiology of an Old Silk Road disease

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Although much is yet to be discovered about Behçet's disease, genetic, environmental and infectious factors are thought to play a role in its development

Behçet's disease is a multisystem disorder named after the Turkish dermatologist, Hulusi Behçet (1889–1948), who recognised and reported in 1937 a triad of symptoms consisting of recurrent eye inflammation, oral ulcers and genital ulcers.[1] The disease had also been alluded to in descriptions by physicians as far back as Hippocrates.[2] Behçet's disease is particularly common in the Far East and the Mediterranean basin, and is frequently noted between the 30th and 45th degree latitudes in Asian and European populations,[3] corresponding to the Old Silk Road, an ancient trading route stretching between the Mediterranean, the Middle East and the Far East. In contrast, this disorder is uncommon in the American continents, Oceania and sub-Saharan Africa.[3]

The underlying pathological process of Behçet's disease is a systemic occlusive vasculitis,[4] resulting in the four major clinical manifestations of (1) recurrent and chronic intraocular inflammation, (2) recurrent aphthous ulcers of the mouth, (3) genital ulcers and (4) skin lesions that may include erythema nodosum, acneiform lesions and cutaneous hypersensitivity thrombophlebitis. The frequency of ocular involvement in Behçet's disease is approximately 70%[4] and is characterised by unilateral or bilateral acute episodes of iridocyclitis with or without hypopyon, and/or panuveitis.[5–7] The classification of ocular manifestations into predominantly anterior uveitis vs predominantly posterior uveitis or panuveitis is important for both therapeutic and prognostic purposes, since inflammation of the posterior segment tends to be stubbornly recurrent with cumulative visual decline over time.[8] Unfortunately, the majority of patients with Behçet's disease and ocular involvement present with recurrence of panuveitis. Clinical experience suggests that the disease is more severe with the risk of losing useful vision higher in men than in women.[9]

Several reports in the literature have described clinical characteristics in large populations of patients with Behçet's disease and uveitis,[9–11] but few have compared features in patients living in different regions of the world. In this issue of the *BJO*, Kitaichi *et al*[12] examine the features of ocular Behçet's disease in patients from an impressive 25 clinical centers in 14 countries of Europe (the UK, Germany and Portugal), the Mediterranean (Italy, Greece, Turkey, Morocco and Tunisia), the Middle East (Jordan, Saudi Arabia and Iran), the Indian subcontinent (India), the Far East (Japan) and Oceania (Australia) ***(see page 1579)***. The authors are to be commended for conducting an international study on such a global scale, and the participating centres are to be commended for their hard work in collecting the data. However, these centres may or may not be representative of each region of the world, since participation in this study was based on return of a descriptive questionnaire survey sent to as many as 132 institutions, representing a return rate of only 19%. Regardless, clinical data were obtained on 1465 patients, and one of the major results of the study was that 23% of patients had a visual acuity less than or equal to 20/200 at final visit. Unfortunately, as the authors point out, variable follow-up of patients makes such a statistic difficult to interpret. Recently, the Standardization of Uveitis Nomenclature Guidelines have recommended that ''final visit'' statistics not be used in reporting outcomes.[13] Instead, the use of rates of a specific outcome (for example, doubling of the visual angle) calculated per ''person-year'' limits the bias of variable follow-up, and also gives the added advantage of subsequent comparability across different studies with different follow-up. Regardless, the distinct impression exists that Behçet's disease remains a blinding disorder despite treatment. Other major conclusions of the study by Kitaichi *et al* included the findings that both the rate of poor visual acuity to less than 20/200 and the rate of panuveitis were higher in men than in women. In general, these results are consistent with those previously reported.[9]

The authors appropriately state that numerous potential biases severely limit the conclusions that may be drawn from their data. These biases include differences in classification of disease, gender proportion, ascertainment of data, follow-up, referral patterns, treatment, access to healthcare and immigration factors in the various countries involved in the study. For example, patients with poor vision were reported more frequently from Iran, India and Japan compared with other countries. Could this be due to genetic differences in various regions, or is it poorer access to healthcare in some countries? Is it the result of differences in treatment strategies? Unfortunately, this study cannot elucidate these issues. With respect to the Japanese data, follow-up periods were significantly longer, and this may have contributed to the poor visual outcome noted. As stated above, this problem may be dealt with by reporting rates of visual loss over time rather than vision at final visit. The conclusions of this study must therefore be considered with the potential biases in mind.

Until very recently, the treatment of Behçet's disease was based on a strategy of inducing immunosuppression in the patient, that is by attacking the pathways of the immune system in a broad and rather non-specific manner using drugs such as corticosteroids and ciclosporin. New anti-inflammatory agents such as infliximab, an antitumour necrosis factor α antibody, now exist that have shown good efficacy in the treatment of rheumatoid arthritis and Crohn's disease.[14] Recently, open-label clinical trials in Japan and Turkey have shown infliximab also to be effective in ocular Behçet's disease,[15 16] and infliximab was approved by the Japanese national health insurance system in January of 2007 for the indication of Behçet's disease with refractory uveoretinitis. Infliximab and other biological agents may be associated with severe systemic side effects, most notably opportunistic infections such as tuberculosis but also exacerbation of congestive heart failure in the case of infliximab.[15 17] Although data on the treatment of Behçet's disease at each participating centre were not included in the study by Kitaichi *et al*,[12] we suspect that the use of powerful biological agents, in countries where available, may improve the visual prognosis in Behçet's disease with severe intraocular inflammation.

Ultimately, if we really understood the pathogenesis of Behçet's disease, we may be able to do even better. However, much is not known. Both intrinsic (genetic) and extrinsic (environmental, infectious) factors are thought to play a role in the

development of this disease. Although the disease is associated with the HLA-B51 locus, not all patients have this genotype.[18] Furthermore, considerable individual variation in disease course and severity is commonly observed. The study by Kitaichi *et al* contributes to our understanding of this complex disease, and we predict it will form the basis of further large-scale international collaborations in the future, including ones involving the development of new therapies.

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Aphakic glaucoma

Aphakic glaucoma: a never-ending story?

A V Levin

Regular screening and continuing research are important in the fight against aphakic glaucoma

Aphakic glaucoma has plagued those who provide ophthalmic care to children ever since paediatric cataract surgery became a reality. It is the second most common cause of paediatric glaucoma,[1] and all children who have cataract surgery remain at risk for life. Its pathophysiology is largely not understood, and there appears to be little if any end in sight on the near horizon. There are many theories as to its causation.

BAROTRAUMA TO THE IMMATURE ANGLE

In support of this theory is the higher frequency of aphakic glaucoma in children who have their surgery at younger ages. Arguing against this theory is the seemingly equal rate of aphakic glaucoma following pars plana lensectomy.

STRUCTURAL CHANGES TO THE ANGLE DRAINAGE COMPLEX

Certainly this makes sense in the ''soft'' paediatric eye and may be supported by a possible lower incidence of glaucoma in pseudophakic eyes, although the latter factor requires many more years of study, and the incidence of glaucoma in pseudophakia seems to rise as the years pass: a rise far above the initial cautious expectations.[2]

GONIODYSGENESIS

Some eyes with aphakic glaucoma do have an angle appearance on gonioscopy very reminiscent of the angle in congenital/infantile glaucoma. Such eyes may even respond to goniotomy. This suggests that there is more that is wrong with the eye than the cataract. If this is true, then perhaps we should see more patients with isolated cataract plus glaucoma before surgery. Such patients may exist but have their ''natural'' glaucoma ''prevented'' by cataract surgery, which is needed promptly to obtain a better vision outcome.

ROLE OF THE VITREOUS

For those who frequently do cataract surgery with primary posterior capsulotomy, especially in younger eyes left aphakic, there is a familiarity with the high frequency of vitreous entry into the anterior chamber. Perhaps the presence of vitreous, even when temporary, can cause a more permanent alteration of aqueous drainage. Gonioscopy techniques do not allow us to assess this possibility well. Again, time will be the judge as we follow the course of pseudophakic patients who had their capsulotomy done after IOL implantation via the pars plana. But these patients are on average older and therefore less at risk for glaucoma.

CHEMICAL FACTORS

Even in adults, when the posterior capsule ruptures during cataract surgery even without vitreous entering the anterior chamber, there is an increase in later glaucoma. Is it the mere exposure of the posterior chamber to the anterior chamber that causes some chemical factor to ''poison'' the angle? Although vitreous excitatory amino acids and other factors have been speculated to have a role in glaucoma, there is much work to be done in this area, and the consistency of the paediatric vitreous is very different from that of adults.

GENETIC FACTORS

Last, and certainly not least, is the unknown role of genetics in determining which child will or will not get aphakic or pseudophakic glaucoma. The aphakic glaucoma does not always seem to segregate in families with heritable cataract, but sometimes it does. The fact that