

# BJO

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## Editorials

### TB or not TB? The perennial question

Tuberculosis is the leading infectious cause of morbidity and mortality worldwide.<sup>1,2</sup> The World Health Organization (WHO) currently estimates that nearly two billion people, or one third of the world's population, are infected by tuberculosis, and that roughly 10% of these infected people will develop clinical disease at some point during their lifetime. This enormous pool of infected individuals results in 8–10 million new cases of tuberculosis and nearly three million deaths due to infection each year. Countries in the developing world, particularly in Africa and South East Asia, bear the brunt of the burden, with more than 95% of new infections and 98% of infection related deaths occurring in these regions. The situation is made even more difficult by the growing human immunodeficiency virus (HIV) epidemic, since simultaneous infection by HIV greatly increases the risk of developing active tuberculosis.<sup>3</sup> At present, 5–10% of all patients with tuberculosis worldwide are also infected with HIV, and in many developing countries tuberculosis is now the most common opportunistic infection in HIV positive patients. These factors, together with poverty, limited resources, and the widespread emergence of multidrug resistant strains of tuberculosis, have led the WHO to declare tuberculosis a global emergency.

Ocular complications of tuberculosis, although less common than systemic involvement,<sup>4,5</sup> are well recognised. Virtually any ocular tissue may be affected, including the ocular adnexa, the cornea, the conjunctiva, the sclera, the uveal tract, the retina, and the optic nerve.<sup>6,7</sup> Uveitis, particularly when accompanied by choroiditis, appears to be the most frequent ocular manifestation of infection. Other findings that can support the diagnosis of tuberculous uveitis include, however, the presence of large keratic precipitates or iris nodules, so called "granulomatous" findings, and retinal vasculitis, which is frequently ischaemic in nature.<sup>8</sup>

The diagnosis of ocular tuberculosis is often problematic.<sup>6,7</sup> The physical findings mentioned above are suggestive but non-specific. Culture or direct histopathological examination of infected tissue can provide definitive proof of ocular infection<sup>9–11</sup> but is often impractical given the risks of intraocular biopsy, particularly in the setting of active inflammation. Polymerase chain reaction based assays performed on ocular fluids provide strong evidence of infection<sup>10–15</sup> but are not well standardised, and are available only at selected centres.<sup>16–18</sup> This leaves chest x ray and purified protein derivative (PPD) skin testing, which, although useful, particularly in patients at high risk of infection,<sup>5</sup> have limited sensitivity and specificity.<sup>11,17–19</sup>

The paper by Sakai and associates that appears in this issue of the *BJO* (p 130) is of great interest, therefore, because it describes the use of a rapid serological test to help support the diagnosis of ocular tuberculosis. The authors studied 15 patients with uveitis and retinal vasculitis—nine with evidence of previous exposure to *Mycobacterium tuberculosis*, all of whom had a positive PPD, one of whom had active pulmonary tuberculosis, and four of whom had radiographic evidence of previous pulmonary tuberculosis; three patients with sarcoidosis; and three patients with Behçet's disease. Each of these patients was tested for the presence of serum antibodies directed against purified cord factor (trehalose-6,6'-dimycolate or TDM), the most antigenic and abundant cell wall component of *M tuberculosis*. All of the patients with presumed ocular tuberculosis but none of the control patients had antipurified cord factor antibodies in their serum. In addition, those patients who had not had previous antituberculosis treatment tended to have higher antibody titres than those patients who had had previous treatment, suggestions that antibody titres might, in some cases, be useful for monitoring response to therapy. These results confirm previously published findings from the same group describing the usefulness of serum antipurified cord factor antibodies to both diagnose and monitor treatment responses in patients with pulmonary tuberculosis.<sup>20</sup> There is some hope, therefore, that such serological assays, if more widely available, could both simplify and improve our ability to diagnose ocular tuberculosis. For now, however, most ophthalmologists will have to depend upon their own clinical skills supported by the time honoured and judicious use of chest x ray and PPD testing.

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## So goes the flow—but not always

The arterial blood supply to the anterior segment of the eye comes primarily from the ophthalmic artery and is carried to the eye by the anterior ciliary arteries and the long posterior ciliary arteries. The usual seven anterior ciliary arteries follow a course along the four rectus muscles; however, the two long posterior ciliary arteries take an intrascleral course and are located deep to the medial and lateral rectus muscles. The anterior ciliary arteries and long posterior ciliary arteries contribute to several collateral circulatory systems including the episcleral limbal plexus, the intramuscular circulation within the ciliary body, and the major arterial circle of the iris root.<sup>1–3</sup> Because of this extensive collateral supplying the anterior segment, ischaemia following strabismus surgery or manipulation of the ciliary arteries is relatively rare.

Anterior segment ischaemia was first documented in experimental animals after ocular surgery.<sup>4–5</sup> Investigators described irregular dilated pupils and iritis after rectus muscle surgery in primates. The first clinical reports of anterior segment ischaemia resulting from ocular surgery date back approximately 50 years.<sup>6</sup> Anterior segment ischaemia has now been reported to be associated with retinal detachment surgery, cyclocryotherapy, and laser photocoagulation. Anterior segment ischaemia associated with strabismus surgery has usually been reported when the surgery involves more than two rectus muscles simultaneously. Although scattered reports have documented the unusual occurrence of anterior segment ischaemia in patients having surgery on only two rectus muscles,<sup>7</sup> anterior segment ischaemia is primarily a complication in adults and is often associated with systemic disease including hypertension, leukaemia, and thyroid disease.<sup>8</sup>

Because the majority of anterior segment blood flow normally derives from the anterior ciliary vessels, anterior segment ischaemia is rarely associated with long posterior ciliary artery disruption. Under normal circumstances the long posterior ciliary arteries are thought to be responsible for less than one third of the blood flow of the anterior segment of the eye.<sup>9</sup> Because the blood supply to the iris is usually sectorial in nature iris blood flow has been felt to serve as an important indicator of the status of the anterior ciliary blood flow in each quadrant. Assessment of the quality of blood flow in the iris has been found to be a useful indicator for the potential risk of anterior segment ischaemia related to strabismus surgery. In the lightly

pigmented iris this can be accomplished with standard fluorescein angiography.<sup>10–11</sup> Iris angiography can demonstrate a delay or absence of iris vessel filling in the quadrant that corresponds to a recently operated on rectus muscle. Iris angiography studies have documented that in normal patients disruption of the anterior ciliary vessels on the horizontal rectus muscles usually does not produce an alteration in iris blood flow that is detectable.<sup>12</sup> In contrast, in both experimental animals and in human patients abnormalities of iris perfusion are frequently seen after disinsertion of one or both of the vertical rectus muscles.<sup>13</sup> Regrettably, standard fluorescein angiography can only be successfully performed on lightly pigmented irides.

In this issue of the *BJO* (p 214) Chan and co-workers have successfully demonstrated that indocyanine green angiography can document iris perfusion changes following strabismus surgery even in the dark iris. Their findings demonstrate that delayed iris perfusion persists for 3–22 weeks following strabismus surgery. For that reason the authors have suggested that an interval of 2–3 months should be allowed to pass before additional strabismus surgery be performed. This is an important observation and provides the strabismus surgeon with another tool to evaluate the patient with strabismus in whom anterior segment ischaemia is thought to be a significant risk. However, one should emphasise that re-establishment of iris perfusion on angiography does not guarantee that further surgery on the rectus muscles will not produce anterior segment ischaemia. The two major risk factors for anterior segment ischaemia are the patient's own susceptibility (in small part age related) and the extent of the strabismus surgery itself.

In patients who are felt to be at high risk for the development of anterior segment ischaemia alternative forms of therapy for the strabismus may be entertained including botulism toxin injection, anterior ciliary vessels sparing surgery, and Wright's modified rectus tuck procedure.<sup>14</sup> One should also note that there is evidence to suggest that anterior segment ischaemia occurs less commonly following a fornix conjunctival incision than with a limbal one.<sup>15</sup>

We should recall that there are data that suggest that anterior ciliary vessels generally do not recanalise after primary rectus muscle surgery. Blood flow from the anterior ciliary arteries disrupted by the surgical procedure is thought to be compensated for by collateral flow.<sup>13</sup> Thus,

iris perfusion studies are not always a direct reflection of the anterior ciliary vessel perfusion in that quadrant. Nevertheless, for the patient who appears to be at high risk for developing anterior segment ischaemia evaluation of iris perfusion would seem to be a prudent part of the preoperative evaluation. Now thanks to the work of Chan and co-workers it appears that such flow studies can be done no matter how pigmented the involved irides.

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