Vasospasm and glaucoma

A 54 year old emmetropic woman is referred to the hospital eye service because her optometrist detected a visual field defect in the presence of normal intraocular pressure using non-contact tonometry. She is otherwise fit and well, is a non-smoker, takes no medications, and has no family history of ocular disease. Examination shows cupping of the optic discs and significant visual field loss. The application of intraocular pressures are never greater than 18 mm Hg at the clinic and during 24 hour phasing, and the clinical diagnosis is low tension—that is, normal pressure, glaucoma (NPG). Why, in the absence of elevated ocular pressure, has this woman developed glucomatous optic neuropathy?

On further questioning, she admits to having cold hands and feet (“my husband says that my feet are always freezing when I cuddle up to him at night”), and also has a history of migraines since her teenage years. What is the relevance of these two vasospastic conditions—Raynaud-like peripheral circulation and migraine—to the case presented above?

Vasospasm is the term used to describe an abnormal vascular responsiveness to common everyday stimuli such as cold, stress, or nicotine. This process may reflect an underlying dysfunction of the vascular endothelium, and has been implicated in other systemic diseases such as coronary artery spasm with angiographically normal or slightly diseased coronary arteries (variant angina) and cerebral vasospasm following subarachnoid haemorrhage.

A number of endothelium derived vasoactive substances play a key role in the maintenance of basal vascular tone throughout the body and in the ocular circulation. Generally speaking, the balance between the relaxing (for example, nitric oxide, prostacyclin) and constricting (for example, endothelin-1 (ET-1), angiotensin II) agents tends towards a state of basal vasodilatation. These vasoactive substances exert their effects on vascular tone by causing relaxation or contraction of the vascular smooth muscle cells, and an imbalance in their levels may result in vascular spasm. Circulating levels of the potent vasoconstrictor ET-1 have been found to be elevated in several vasospastic conditions including Raynaud’s disease, migraine, variant angina, and subarachnoid haemorrhage.

Flammer et al first introduced the concept of vasospasm to glaucoma, particularly NPG. In a series of papers this group initially concentrated on ocular vasospasm (including choroidal vasospasm) but later they expanded on this idea to include more widespread evidence of systemic vasospasm in glaucoma, such as silent myocardial ischaemia in NPG patients. Others have shown an impaired digital circulatory response to cold provocation and a higher than expected prevalence of migraine in NPG.

Two recent papers show that patients with NPG have elevated systemic plasma levels of ET-1 and an abnormal postural ET-1 response. An impaired endothelium mediated vasodilatation to intra-arterial acetylcholine infusion in forearm blood flow has also been demonstrated in NPG. These findings would suggest that the “vascular” abnormality in NPG is not just confined to the ocular circulation, and may indicate that the eye is just one manifestation of a more generalised vascular disorder characterised by endothelial cell dysfunction.

There is evidence that some glaucoma patients may show a reversible form of ocular vasospasm in that ocular blood flow (and possibly visual function) improves with the use of recognised vasodilators such as carbon dioxide and intravenous acetazolamide. Some long term observations on the concurrent use of calcium antagonists in glaucoma suggest a protective effect on the visual field in some patients. The Vancouver group has previously reported that vasospasm may equally be a feature of both NPG and the high pressure form of this disease—primary open angle glaucoma. They noted that vasospastic glaucoma patients appeared to be sensitive to the level of intraocular pressure in that they observed a relation between the height of the ocular pressure and the amount of visual field loss in a group of vasospastic patients, but that this relation did not exist in non-vasospastic patients. In the current issue of the *BJO* (p 862) Broadway and Drance repeat their observation that vasospasm occurs with equal frequency in both the normal and high pressure forms of open angle glaucoma. However, the main finding of their paper is that glaucoma patients with the so called focal ischaemic type of optic disc appearance tend to be women with some form of vasospasm (history of cold extremities, migraine, or reduced digital circulation following cold provocation).

How does this vasospasm relate to optic disc damage, especially to localised rim notching? Is this due to some form of focal ischaemia in the ciliary circulation (capillary network or larger branches of the short posterior ciliary vessels) of the anterior nerve head? Why does this form of damage typically occur at the superotemporal and inferotemporal poles of the optic disc? What are the anatomical and physiological factors that predispose to such damage? Does vasospasm in some way interfere with local autoregulatory mechanisms in the vasculature of the...
nerve head? Is the vasospasm reversible? These are questions which require further investigation. Of particular importance is the recent development of an animal model of optic nerve head ischaemia with repeated periocular injections of ET-1. This results in vasoconstriction, a reduction in blood flow, and glaucoma-like topographic changes in the optic nerve head. Such a model might provide us with a better understanding of the connection between vasospasm and glaucoma.

Vasospasm or vascular endothelial dysfunction appears to be a feature of glaucoma in some patients. It may only affect a small proportion of the total glaucoma population, but in trying to understand the connection between vasospasm and optic disc damage, we will gain insight into the pathogenesis and management of one form of glaucomatous optic neuropathy. Perhaps then the relevance of Raynaud’s disease and migraine to the NPG case history described above will become clear.

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Serological tests for monitoring and predicting disease severity, course, and outcome of autoimmune intraocular inflammation

Around 50% of cases of uveitis are classified as idiopathic, while many of the others are associated with or form part of other disease entities. Idiopathic uveitis comprises a spectrum of CD4+ T cell mediated MHC class II restricted, chronic autoimmune intraocular inflammatory conditions, the underlying immunological effector mechanisms of which have many features in common with systemic conditions associated with intraocular inflammation—for example, sarcoidosis, Behçet’s disease, seronegative spondyloarthropathies, and multiple sclerosis. Therapy for these conditions must be tailored to treat both ocular and systemic disease, although successful immunosuppression for the ocular inflammatory component can be achieved using the same approach as for idiopathic chronic intraocular inflammation, especially if the systemic component is inactive. Recognising whether intraocular inflammation is idiopathic or associated with systemic disease either at the time of presentation or in the future is difficult. For example, the term “intermediate uveitis”, which includes pars planitis, not only embraces an undefined number of disease entities, but is frequently associated with underlying systemic diseases such as sarcoidosis and multiple sclerosis. Thus a major management problem which commonly arises is because the presently available clinical tests cannot predict whether patients with intermediate uveitis have or will develop an associated systemic disease. It is well recognised that in sarcoidosis up to 30% of cases present with uveitis, sometimes years before the onset of clinical signs of the disease. However, this diagnostic dilemma should not cause delay in instituting early and adequate immunosuppression for sight threatening disease.

The management of intermediate uveitis, or indeed any autoimmune chronic intraocular inflammatory conditions, centres on two broad issues: firstly, what is the likely course of disease and in particular, is there any evidence of underlying systemic disease; and secondly, when is immunosuppressive therapy required and for how long?

Klok et al in this issue of the BJO (p 871) have shown that in a cohort of patients with presumed idiopathic intermediate uveitis, elevated serum IL-8 levels correlate with severity of disease and, in addition, testing for IL-8 may predict who will develop systemic diseases, such as sarcoidosis. Often a decision to immunosuppress is based on the natural history (that is, known poor prognosis) of the presenting clinical entity such as serpiginous choroiditis, and presence of sight threatening disease—for example, cystoid macular oedema (CMO) and/or choroiditis or vasculitis affecting the macula or optic nerve. However, as is the case with intermediate uveitis the course of disease varies between patients and is unpredictable, and unless complications, such as CMO, are present when the patient...
Although the present data suggest that high IL-8 levels may be difficult. Furthermore, despite current therapeutic strategies using combination therapy, treatment is still complicated by side effects and/or unresponsiveness and by relapses on dose reduction. The latter is particularly apparent because the only method of monitoring disease activity is by clinical assessment, which may not reflect the true level of underlying immune activation.

We, therefore, urgently need to develop methods of assessing immune activation, predicting outcome of disease and monitoring immunosuppressive therapy so as to anticipate relapses and reduce side effects by dose adjustments without loss of efficacy. There have to date been several preliminary reports of immunological tests which have been used to monitor therapy because of their possible correlation with inflammatory activity—for example, antineutrophil cytoplasmic antibodies (ANCA) titres in ANCA positive systemic vasculitides and ANCA positive uveitides, as well as in Wegener’s granulomatosis. Other tests include markers of CD4 T cell activation of this cell subset (which may be reduced during immunosuppression) or the activation products which these cells produce (soluble IL-2r) since they can be identified in serum. More recently, raised levels of the immunomodulatory molecule IL-1ra have been found in ocular Behçet’s disease, indicating that the therapeutic effect may be mediated by this. All these studies remain largely unconfirmed or have not been adequately studied longitudinally and therefore currently their role in predicting disease severity remains unclear.

Routine examination for the detection of systemic disease in chronic intraocular inflammation is frequently unrewarding. Measurements of inflammatory activity including acute phase reactants, which can be sensitive indicators of systemic inflammation (for example, C reactive protein (CRP)), are generally within normal values in uveitis, as confirmed in this present study. More recently, indicators of polymorphonuclear (PMN) activation, including PMN elastase and calprotectin, have been found to be raised in untreated uveitis and potentially may be used to monitor uveitis. IL-8 is a C-X-C chemokine interleukin produced by a variety of cells including mono- cytes and macrophages and has two important roles, particularly when considering the underlying pathology of uveitis and other granulomatous inflammatory diseases, such as sarcoidosis. The first is neutrophil activation, in which IL-8 combines synergistically with TNF-α facilitating leucocyte adhesion and diapedesis; the second is as a chemoattractant particularly for non-specific naïve T cells. The overall effect is to increase the access of effector cells into target tissue sites of inflammation. It is not surprising, therefore, that raised serum IL-8 levels are found in patients with uveitis. The interest of the data of Klok et al is that a significantly large number of patients with intermediate uveitis and/or known sarcoid uveitis compared with other uveitides had raised IL-8 levels, although the study was not constructed specifically to measure outcome or to relate severity to disease activity. It also showed that IL-8 levels correlated with disease activity and the development of sarcoidosis and multiple sclerosis. Are we now near to answering some of the patients’ major concerns?

Predicting the course and outcome of disease (whether treated with immunosuppressive therapy or not) is unlikely to be available based on a single analysis of IL-8 levels. Although the present data suggest that high IL-8 levels correlate with disease activity, further study is required to provide definitive evidence that these levels vary with immunosuppression or disease activity. Furthermore, additional data are also required to provide greater predictability for IL-8 testing in systemic disease risk assessment. Future developments which incorporate a series of tests—for example, IL-8 measurement in combination with genetic susceptibility markers, may offer better predictive outcomes for individual patients, similar to strategies under development for systemic sarcoidosis which involve “genetic fingerprinting” via HLA association and specific allelic polymorphisms. These approaches can be adopted for ocular inflammatory disease. In addition to the association with HLA-A28 and intermediate uveitis, recent reports suggest that patients who are HLA-DR15 positive and have intermediate uveitis have an increased incidence of systemic findings of other diseases linked to HLA-DR15, including multiple sclerosis. If we can identify possible genetic polymorphisms, such as those recently reported for the HLA linked LMP2 locus polymorphisms which determine development of HLA-B27 acute anterior uveitis (AAU) in patients with ankylosing spondylitis, in combination with immunological tests such as serum IL-8 levels, we could see the development of individual risk assessment which may predict not only severity but also course and outcome of disease.

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