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Editorials

Retroviruses – a clue to autoimmunity?

Yamaguchi and colleagues describe, in this issue of the journal, the association of Graves' disease with human T lymphotropic virus type 1 (HTLV-I) uveitis in a population of Japanese patients. HTLV-I is a retrovirus of the oncovirus subfamily and is notable for being the first retrovirus to be specifically linked to malignancy in humans – namely, adult T cell leukaemia (ATL).^{1,2} It has a worldwide distribution with clustering in specific geographical areas which include southwest Japan and the Caribbean, but a very low incidence in Europe and North America. For example, in a prospective series of 245 ethnically diverse patients attending a uveitis clinic in London, only one patient of Afro-Caribbean origin with recurrent acute anterior uveitis proved seropositive for HTLV-I (M Mochizuki, personal communication). Most ophthalmologists in non-endemic countries like the United Kingdom are unlikely even to meet an HTLV-I positive patient, let alone see this clinically distinct type of uveitis, so how significant and important is this new clinical association?

In addition to its association with ATL and uveitis, HTLV-I is causally linked to specific neurological diseases – namely, HTLV-I associated myelopathy/tropical spastic paraparesis (HAM/TSP). A consistent feature of all of the diseases associated to date with HTLV-I is the presence of T cell activation, particularly CD4⁺ cells, as demonstrated by the enhanced expression of the interleukin 2 receptor α chain (IL-2R) on the cell surface. HTLV-I infection results in the development of specific antibodies in serum (and other fluids – for example, cerebrospinal fluid) but, in addition, proviral DNA is incorporated into the genome of lymphocytes. In ATL, this integration is monoclonal and occurs only in transformed leukaemic cells,³ whereas in other HTLV-I related diseases the integration is polyclonal, leading to an expanded population of activated T cells. The CD4⁺ cell is considered to be the lymphocyte fundamentally involved in the induction and propagation of uveitis and other autoimmune diseases.⁴ The factors which determine whether this T cell expansion is monoclonal leading to ATL, or polyclonal and associated with non-malignant disease are, as yet, undefined. This study on Graves' disease suggests that age and sex may be valuable clues.

Like ATL, the highest incidence of HTLV-I associated uveitis occurs in younger patients.⁵ There are, however, significant sex differences in the diseases, with HTLV-I associated ATL being more common in men⁶ (though a more recent lymphoma series from the Caribbean did not confirm this⁷), whereas, in Yamaguchi's report and others,⁸ HTLV-I uveitis associated with Graves' disease occurs almost exclusively in women. Could sex account for the pattern of disease, or is the explanation related to the mode and timing of infection with HTLV-I? Most authorities consider that

vertical transmission through breast feeding is the major mode of HTLV-I infection, with less frequent transmission through sexual contact (predominantly from men to women), blood products, and, increasingly, intravenous drug use. In endemic areas, the prevalence of seropositivity in men rises in the second and third decades to around 20% but thereafter remains fairly stable. This is in marked contrast to women in whom there is a linear increase in seropositivity throughout the reproductive years and beyond, rising to as high as 50% by the ninth decade,⁹ a pattern more consistent with a horizontal mode of transmission. Does early, vertically acquired HTLV-I lead to ATL, whereas later, horizontally acquired disease result in autoimmune diseases such as uveitis and Graves' disease? One consequence of these major sex differences is the need for very careful matching of sex and age in control populations when interpreting HTLV-I serology.

Since Graves' disease preceded the development of uveitis in all patients in this series by a minimum of 7 months, it would be of considerable interest to know their HTLV-I status when initially hyperthyroid. The intact blood-retinal barrier can only be breached by activated lymphocytes and it may be that through HTLV-I induced lymphocyte activation, immunocompetent CD4⁺ lymphocytes enter the eye and initiate uveitis which thereafter becomes self-perpetuating.

How is thyroid dysfunction linked to HTLV-I associated uveitis, since Graves' disease does not predispose to other forms of uveitis? The susceptibility to different patterns of HTLV-I associated disease has been linked to HLA haplotype,¹⁰ and similarly Graves' disease shows patterns of HLA susceptibility.¹¹ In general, there is an increased incidence of DR3 in autoimmune diseases, with a relative risk of 3.7 for Graves' disease, particularly when also associated with A1 and B8. DQA1*0501 has also been closely associated with Graves' disease, occurring in 66% of patients compared with 36% of controls.¹² ATL and HAM are associated with differing HLA haplotypes,¹³ and, furthermore, the degree of immune responsiveness to virus antigens can be separated into high and low responders, the former being associated with HAM and the latter with ATL. Are Graves'/HTLV-I uveitis patients also high responders?

Another possible though less likely link may be in the drug treatment of Graves' disease. All patients in this series received methimazole which, like carbimazole, is known to have mild immunosuppressive properties. It would be of value to know what antithyroid therapy was in use when HTLV-I uveitis presented, and to compare this with HTLV-I positive Graves' patients who have not developed uveitis.

For most ophthalmologists, HTLV-I uveitis will remain a

clinical curio which they are unlikely to encounter. It does, however, offer potential insight into the mechanisms of initiation and propagation of uveitis and other autoimmune disease, and confirms the importance of the CD4⁺ T cell in this process. The explanation as to why some individuals develop malignancy and others autoimmune disease is eagerly awaited.

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Changing concepts in ptosis surgery

In this issue of the journal, the article by J R O Collin and B A O'Donnell draws our attention to a changing concept in the surgery for blepharoptosis. There are many and various techniques for the management of the adjustment of lid height, either for practical optical reasons or for purely cosmetic reasons.¹

An initial foray into the literature allows an easy understanding of the principles behind lid height management, and to the uninitiated the procedures appear to be relatively straight forward. Line diagrams, cadaver dissections, and the occasional prepared coloured slide give a general overview of the work of the ptosis surgeon and an appreciation of its apparent simplicity.

However, in reality there are many frustrated junior and senior doctors who are being confronted with the 'Red Sea' of blood that despite many a prayer does not part, and the final surgical result is indicative of lack of understanding in dissecting techniques. Surgeons who specialise in lid and periorbital procedures have often quite varied approaches to what appears to be a common end result, but despite personal differences and often heated discussion, one constant requirement remains - that is, knowledge of anatomy, which must be combined with a consistent dissecting technique and the ability to know where one is within the 'lid sandwich'. Once this has been mastered, then the various surgical doctrines can be adapted to suit virtually any surgeon. Precise repositioning of a retracted levator aponeurosis or the precise excision of levator and Müller muscle are the features of a successful surgical technique.

However, despite relative consistency, there are patients who do not conform to the standard pattern, and many of the pathologies listed in the article by Collin and O'Donnell exemplify this problem. Such conditions range from degenerative and dystrophic extraocular muscle pathologies to endocrine imbalance resulting in dysthyroid ophthalmopathy. The upper lid can vary in position quite dramatically and with abnormal muscle function the standard ground rules of levator surgery often have to be abandoned.

The adjustable suture technique described offers an expansion in the range of options that the surgeon can call upon when controlling lid height. This is not a new concept, because when the archives are dusted down and examined it is easy to find theories on adjustable suture techniques encompassing all the extraocular muscles dating back a substantial amount of time.^{2,3} It is relatively recently⁴ that the strabismus surgeons have presented the profession with consistent repeatable and successful adjustable suture techniques. The main difference between their current success and their predecessors' failure is the quality and standard of materials available.

The current article underlines the success obtainable with modern equipment, which we often take for granted. The particular style of alloy needle coupled with absorbable strong, yet sleek running suture material is very much a modern development, and I think many of our predecessors would have been well pleased to have had this type of material at their disposal. It is therefore much easier to adopt the principle of postoperative manipulation of soft tissue in an expanding group of patients. The technique, however, may be limited to the patients who are responsive, cooperative, and relaxed and, although the pathology may indicate adjustable suture technique as being the most favourable form of surgery for a reasonable outcome, we must not forget the patients and their wishes and demands. The adjustable suture ptosis surgery technique undoubtedly adds to the surgeon's armoury for lid work.

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