MAILBOX

Use of polymerase chain reaction in detection of Mycobacterium tuberculosis complex DNA from vitreous sample of Eales’ disease

Eales, T. — Eales’ disease, first described by Henry Eales in 1880 is a primary retinal perivasculitis that predominantly affects the peripheral retina of young and otherwise healthy adults in the age group 15–40 years. Of the several aetiologies proposed, most favoured are tuberculosis and hypersensitivity to tuberculin protein.1 Since polymerase chain reaction (PCR) using primers for the insertion sequence of IS6110 consisting of upstream primer: 5’ CCTGCGAGCGTAGGCTTCG3’ and downstream primer: 5’CTGCAGGCCGGCTCCTCG 3’ coding for 123 bp product, has found a universal acceptance for detection of Mycobacterium tuberculosis complex DNA in clinical specimens,2 we applied it on vitreous fluid samples obtained from clinically diagnosed patients with Eales’ disease and controls (undergoing vitreous surgery for proliferative diabetic retinopathy and proliferative vitreoretinopathy).

Uncontaminated vitreous fluid from 12 cases of Eales’ disease and 45 non-Eales’ disease control patients collected at the beginning of vitrectomy were subjected to PCR using IS6110 primers for the presence of M tuberculosis complex DNA.1 PCR was found to be specific and sensitive enough to detect 2.5 pg of Mycobacterium tuberculosis complex DNA. Five (41.6%) among 12 vitreous fluid samples from Eales’ disease (Fig 1) and only one (2.2%) out of 45 vitreous fluid samples from the control group were positive by PCR and this difference was statistically significant (Pearson-χ² < 0.001). Vitreous fluid from both groups of patients did not reveal the presence of acid fast bacilli by direct smear and culture by standard conventional techniques.

The presence of M tuberculosis complex DNA in a statistically significant number of vitreous fluid samples of Eales’ disease patients compared with the control group leads us to hypothesise the presence of sequestrated Mycobacterium in the eyes of Eales’ disease patients and a probable role of this bacterium in the pathogenesis of this enigmatic clinical condition.

Vertical cup/disc ratio in relation to optic disc size

Eales, T. — In a recent paper,1 the vertical cup/disc ratio (CDR) in relation to optic disc size was evaluated in order to aid in the identification of optic discs with glaucomatous optic neuropathy. Two methods of using the vertical CDR were assessed, one method independent of disc size and the other dependent on disc size.

With the disc size independent method, for a group of patients with primary open angle glaucoma (POAG) and a control group, the authors calculated the vertical CDR and, based on a histogram plot of the control group, concluded that the vertical CDR is not normally distributed. An empirical cut off for the upper limit of normal was taken as the 97.5% percentile. When this test criterion (vertical CDR = 0.682) was applied to the two groups, this method yielded a sensitivity of 56.6% and specificity of 97.7% for the identification of glaucomatous optic discs. The conclusion that the vertical CDR is not normally distributed is not disputed (Chernoff-Lehmann test, χ² < 0.10). However, the optimal vertical CDR may be selected rationally (rather than arbitrarily) by plotting sensitivity against (1 – specificity) to produce a receiver operator characteristics (ROC) curve (Fig 1A). The optimal test criterion is the point on the ROC curve furthest from the line of zero discrimination; from the authors’ data, the optimal test criterion is a vertical CDR cut off of 0.587 (sensitivity 86.6%, specificity 87.5%). Having rationally selected the optimal test criterion, its value as a clinical aid is best assessed by the predictive power of a positive test (rather than by isolated sensitivity and specificity values). This predictive power (V+) is the proportion of true positives by reference test) to total positives (true positives + false positives) and is a function not only of sensitivity and specificity but also of prevalence. V+ may be calculated from: V+ = l1((S − 1) + (P − 1)/NP)1, where N = specificity, S = sensitivity, and P = prevalence. The prevalence of glaucoma varies according to the population studied and the criteria used as the reference test, but is generally considered to be approximately 2% in adults older than 40 years of age.1,2,3,4,5 Since the authors used the upper waist of the 95% confidence interval as a straight line to calculate a linear intercept of −0.87. The simple relation between vertical cup diameter and vertical disc diameter was then used to calculate the upper limit of the 95% confidence interval of the vertical CDR as: (0.193 vertical disc diameter) = 0.87 (vertical disc diameter). When this test criterion was applied to the two groups, sensitivity and specificity for the identification of glaucomatous optic discs were respectively 62.3% and 98.9%. The optimal confidence interval may be selected rationally using an ROC curve constructed from different confidence intervals: the optimal test criterion is a confidence interval of 72% (sensitivity 90.2%, specificity 92.3%) (Fig 1B) which yields a predictive value, V+ = 19.3%. The predictive value of the authors’ test criterion of a 95% confidence interval is 53.6%.

We therefore agree completely with the authors that optic disc biometry provides useful data in the identification of glaucomatous discs: the authors’ work has shown that the disc size dependent method (V+ = 19.3%) is superior to that which is disc size independent (V+ = 12.4%). Their disc size dependent

Figure 1 Results of PCR using IS6110 primers on vitreous aspirates of Eales’ cases. Lanes: 1, case 1 (positive); 2, case 2 (negative); 3, case 3 (negative); 4, case 4 (positive); 5, case 5 (positive); 6, positive control (H37Rv); 7, negative control (reagents); 8, molecular weight marker (Pha x 174 Hind I digest).

Figure 1 Receiver operator characteristics curves for vertical cup/disc ratio (CDR) (A) and confidence intervals of vertical CDR — vertical disc diameter regression analysis (B). Open circles = sensitivity, 1 − specificity) points; solid circles = optimal test criteria. Diagonal line indicates zero discrimination. CDR(v) = vertical CDR; CI = confidence interval.
method is reminiscent of the concept of the “rim index” (observed neuroretinal rim area/expected neuroretinal rim area) first described in 1991 by Montgomery.  

In general, the arbitrary selection of test criteria yield better predictive values but poorer sensitivity. Therefore, optimal selection of test criteria using ROC curves improves sensitivity but reduces predictive power. We therefore consider it important to appreciate that, in screening for a low prevalence disease with important health implications such as glaucoma, test criteria must be optimised to maintain a high sensitivity and steps taken to cater for a false positive rate of at least 80% which is inevitable in these circumstances.

| Table 1 | Case detection per 1000 population using cut off values given by Garway-Heath et al  
| Disc size | True positives | False positives | False negatives |
| Independent | 11.3 | 22.5 | 8.7 |
| Dependent | 12.5 | 10.8 | 7.5 |

| Table 2 | Case detection per 1000 population using cut off values given by Barr and Nolan |
| Disc size | True positives | False positives | False negatives |
| Independent | 17.3 | 12.2 | 5.0 |
| Dependent | 18.0 | 7.5 | 2.0 |

**Suggestion for IL-2 treatment of conjunctival squamous carcinoma**

EDITOR,—We refer to a recent publication of Poole, discussing the incidence of conjunctival squamous carcinoma in Tanzania, notably in HIV affected patients. We have extensively studied a similar condition (bovine ocular squamous carcinoma) with a comparable genesis in veterinary cases, in the Harare area (Zimbabwe). We treated such cases with intralesional IL-2 injections of U 90-107 (Chiron) over 10 days. A large number of remissions and in 67% of the cases even complete cures (20 month observation period) were obtained. In fact, even tumours of over 6 cm in diameter may regress completely with this therapeutic regimen. This form of treatment is cheap, not-toxic, effective, and feasible even in basic situations. It might be worth considering such treatment in human patients, obviously with the appropriate pre-requisites.

JAN-WILLEM KOTSEN  
WILLEM DEN OTTER  
Department of Cell Biology and Histology, Utrecht University, Utrecht, Netherlands  
Correspondence to: Willem Den Otter, Department of Cell Biology and Histology, Utrecht University, PO Box 80.176, 3508 TD, Utrecht, Netherlands.


**Reply**

EDITOR,—I thank Koten and Den Otter for their interest in my paper. Their experience with intralesional interleukin-2 in the treatment of bovine ocular squamous carcinoma makes very interesting reading. Regional low dose administration of interleukin-2 appears to be safe and is already used in other specialities: systemic toxicity is reduced and a high local concentration is achieved, and most adverse reactions are self limiting and can be managed on an outpatient basis. An appropriate clinical trial would be valuable if their good results in the bovine condition could be replicated in the human one.


**Reply**

EDITOR,—We thank Barr and Nolan for their observations. We agree that the ROC curve is indeed a useful way of presenting such data, allowing a ready comprehension of the relation between sensitivity and specificity over a range of possible cut off values. However, the stated “optimal test criterion”? is the point on the ROC curve furthest from line zero which is an oversimplification. The optimal test criterion depends entirely on circumstances in which the test is applied, not on an exact mathematical concept. Specifically, in this context, the estimation of the cup/disc ratio (CDR) is not a “test” performed in isolation. The vast majority of new glaucoma referrals to the hospital eye service are from optometrists, who perform a number of tests for glaucoma: the vertical cup-disc ratio is not a “test” performed in isolation.

In general, the arbitrary selection of test criteria yield better predictive values but poorer sensitivity. Therefore, optimal selection of test criteria using ROC curves improves sensitivity but reduces predictive power. We therefore consider it important to appreciate that, in screening for a low prevalence disease with important health implications such as glaucoma, test criteria must be optimised to maintain a high sensitivity and steps taken to cater for a false positive rate of at least 80% which is inevitable in these circumstances.
It would be hard to justify experimental treatment in an advanced condition where local excision or enucleation might be life-saving. A careful trial in the treatment of early conjunctival tumours, however, with vigilant follow up (sometimes difficult in an African setting), might be worthwhile. Another application of their useful work, when attempting to preserve an otherwise normal eye, might be to inject interleukin-2 at the excision margins after tumour resection, to prevent recurrence.

To be of use in Africa any treatment needs to be cost effective. One vial of recombinant interleukin-2 contains 18 million units and costs £140. If this could be used for several patients the cost might not be prohibitive. To put this cost in perspective, many patients I saw in Tanzania could not afford the £15 for cataract surgery.

T R G POOLE
Department of Ophthalmology, St Thomas’s Hospital, Lambeth Palace Road, London SE1 7EH


BOOK REVIEWS


This text is written by optometrists and its main strengths are as a practical guide to vision assessment and refraction in infants and young children. It is a comprehensive review of the up to date literature on visual development and assessment in the child. A chapter on normal child development emphasises that vision develops a parallel with motor, sensory, social, and language skills. Practical tips to help gain the child’s and parent’s confidence and cooperation in examination and assessment abound. (We must always ask and explain the toddler’s role in the examination if we are to expect cooperation and a meaningful result.)

There are a few omissions and inaccuracies in the medical section. A succinct review of congenital and childhood cataract management fails to mention examination of the red reflex with the direct ophthalmoscope for cataract as part of the routine neonatal examination of all newborns. Many paediatric ophthalmologists now utilise intraocular lens implants in the routine surgical management of childhood cataract, particularly after 1–2 years of age.

This book will be invaluable as a guide to vision assessment in childhood for optometrists, orthoptists, paediatricians, and ophthalmologists. The ophthalmologist will also find it an up to date source of the currently available knowledge on the development of vision in the infant and young child.

W H CHURCH


Ophthalmology is by definition a visual subject and this is evidenced by the fact that some of the best selling books in ophthalmology are colour atlases. No one who always preferred to read comics at school rather than books I therefore looked forward to reading through this new atlas of glaucoma. The ranging line drawings and the pictures of daily colour photography, viewing the same drainage angles with different examination techniques. Finally, it was nice to browse through the rest of the book looking at the illustrations and accompanying text, as there were some very good illustrations that I had not previously seen in other books or publications.

The book does suffer slightly from the fact that it has multiple authors, are therefore formatting of the chapters is rather variable, which the authors acknowledge in the foreword. Some of the chapters have, for an atlas, rather too much text and too few pictures. In the chapter on filtration surgery, all of the illustrations are in black and white, which rather lets the book down, compared with the excellent colour illustrations in the rest of the book. There are also two irritating features like incomplete references and mislabelled illustrations. However, these are minor details and should be easily remedied in the next edition.

In conclusion, this is a book I would certainly recommend to trainees in ophthalmology and those with an interest in glaucoma because of some of the excellent illustrations, which are a good aid to learning.

P T KHAW


This textbook is intended to provide the ophthalmologist with an up to date source of information on medical and surgical vitreoretinal disease. The book follows many others in being subdivided into basic sciences covering embryology, anatomy, and physiology followed by a further section on techniques of fundus examination, angiography, ultrasonography and electrophysiology. Finally, and fortunately, the most extensive section is clinical.

The editors have to be congratulated in ensuring that a multiauthored textbook manages to be consistent in its style. The quality of the illustrations is extremely high, there are many colour photographs which add, rather than detract, from the text. An innovation in this textbook is the use of highlighted paragraphs which the authors call “pearls” or “controversial points”. Some readers might find these somewhat distracting but the reviewer found them to be very useful. Obviously a book running to 690 pages cannot claim to be fully comprehensive but there were very few obvious omissions and there are useful references at the end of each chapter. A very useful appendix is included which summarises the major multicentre trials as they pertain to vitreoretinal disease. This section would be extremely helpful for juniors in training and those practising ophthalmologists who perhaps have not read the trials in detail.

Inevitably there are minor quibbles in such a book; for example, the management of retinal detachment fails to mention the D-Ace procedure, a fault found in many American textbooks. It is also a pity that the proof reading was not entirely up to scratch—for example, page 190 the final paragraph ends in mid sentence.

Overall, however, this textbook is a valuable addition to the ophthalmic literature and the presentation is certainly different enough to make it an essential purchase for all departmental libraries and, if the pricing is correct, I am sure many ophthalmologists will buy a personal copy.

P S BAINES


Fear of eye disease is a major anxiety of individuals with diabetes. Monitoring the eyes of these individuals is a major anxiety of those charged with managing their diabetes. The situation is complicated by the fact that advanced ophthalmic pathology may have no effect on current visual function, but denied timely treatment it is likely to progress to irreversible visual loss. The need for efficient and reliable eye screening is therefore very considerable, as also is the need for the diabetic individual to participate in his own care and management.

This attractive and refreshingly unpretentious little volume embraces these central issues relating to the monitoring and treatment of diabetic eye disease in a concise “Introduction and Aims” chapter. It proceeds to summarise the classification and natural history of diabetic retinopathy followed by a description of ocular examination and a discussion of options for methodology and organisation of screening. The next two sections consider the indications for referral from the primary screener to the specialist ophthalmologist, and the management of diabetic retinopathy. Then, true to the pragmatic theme of the book, it concludes with a very useful chapter on management of visual loss, followed by an annotated picture.
gallary of non-diabetic eye abnormalities which may be encountered on funduscopic examination.

The layout of short chapters and bullet pointed lists is excellent and easy to read and refer to. The liberal use of panels listing key points or summarising information is also very helpful. The widespread use of (a wide variety of) illustrations makes the book attractive to look at. The quality of reproduction of some of the retinal images, however, will be a particular disappointment to those who do not already know what they are trying to illustrate.

Bill Alexander is to be congratulated on producing this thoughtful and informative book at a time when the development of a variety of models for provision of diabetic services is contemporaneous with heightened awareness of a need to set and observe services is contemporaneous with heightened awareness of a need to set and observe. The quality of reproduction of some of the retinal images, however, will be a particular disappointment to those who do not already know what they are trying to illustrate.

Bill Alexander is to be congratulated on producing this thoughtful and informative book at a time when the development of a variety of models for provision of diabetic services is contemporaneous with heightened awareness of a need to set and observe services is contemporaneous with heightened awareness of a need to set and observe.
Vertical cup/disc ratio in relation to optic disc size

D B BARR and D J NOLAN

*Br J Ophthalmol* 1999 83: 994
doi: 10.1136/bjo.83.8.994a

Updated information and services can be found at:
http://bjo.bmj.com/content/83/8/994.2

This article cites 9 articles, 3 of which you can access for free at:
http://bjo.bmj.com/content/83/8/994.2#BIBL

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/