CORRESPONDENCE

Acanthamoeba keratitis: risk factors and outcome

EYEROS—The paper by Illingworth and colleagues was useful since it identified: firstly, that the occurrence of Acanthamoeba keratitis rose substantially in the 1990s, a fact known to eye institutes in the UK, but contested by the College of Optometrists; and, secondly, that we are on the right track therapeutically when assessing the contribution of a biguanide antiseptic and a diamidine, in the form of propamidine isethionate.

There were, however, two major issues in the contribution which we found confusing. Firstly, the occurrence of Acanthamoeba keratitis in Koch's postulates fulfilled and viable Acanthamoeba detected from scrapes of corneal epithelium. The remainder were diagnosed on clinical criteria alone. It is misleading in this context how to include responses to the regimen of PHMB or Brolene, or a combination of these, since both compounds have a broad spectrum antimicrobial activity. Responsiveness or not to such an agent cannot be considered as evidence for the presence or absence of a specific microbe.

Having amassed considerable experience in the cultivation of Acanthamoeba and other free living amoebae from corneal tissues, which have often been exposed to a cocktail of antibiotics and other drugs, we have considerable empathy with the authors' difficulties in identifying the amoebae from the standard clinical samples.

We routinely examine the scrape, unstained and mounted in a buffered saline solution, using bright field or phase contrast microscopy. Our success rate with this method is very high with 13/20 (65%) followed by culture and histology. This rapid diagnosis permits rational medical therapy to be instituted without delay.

Secondly, only one patient in the series became infected with Acanthamoeba (Koch, Brolene, or both). The authors state that there were no other toxic effects observed. They do not, unfortunately, provide details of the concentration of PHMB used (one presumes it is that described in previous papers) or the frequency of use of the drugs in their patient group. PHMB is known to have an affinity for anions such as the chloride ions present in a saline solution. PHMB can also interact with various plastics or with non-acid aged glass. These factors may reduce considerably the actual concentration of the compound delivered to the ocular surface. We believe that formulation and storage of this drug is thus of considerable importance. The frequency of use may affect the clinical picture of Acanthamoeba keratitis or determining toxicity profiles.

The biguanide chlorhexidine has a similar albeit weaker Acanthamoebicidal effect as PHMB, although it was the antiseptic of choice when assessing therapeutic response to an Acanthamoeba infection or determining toxicity profiles.

Despite rigorous follow up, no iatrogenic effects were noted. Chlorhexidine salts at concentrations of 0.2% have been subjected to intensive toxicological investigation by dermatologists and dentists; the compound is also fairly innocuous to the external eye. It should be noted that no such data are currently available for PHMB. Perhaps for this reason alone, it would be more appropriate to consider chlorhexidine as the first choice of therapy, possibly in combination with Brolene, for the treatment of Acanthamoeba keratitis.

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Reply

EYEROS—Koch's postulates were intended to be used to prove a causal link between a micro-organism and a disease entity. In the case of Acanthamoeba keratitis, a number of previous reports in the literature have already established this link. It is true of many other infectious diseases where it is considered acceptable in clinical practice to make a firm diagnosis in the absence of positive culture. While the results of the own clinical picture of Acanthamoeba keratitis is rather typical: with increasing experience it is frequently possible to make the diagnosis at presentation to a corneal speciality clinic, and start treatment before culture results are available. Positive culture is desirable, but not essential for diagnosis. One of the purposes of our paper was to offer some guidance to clinicians who encounter patients whom they suspect may have Acanthamoeba keratitis. In this context our experience of eyes that have clinical features of the disease but a negative culture is useful, and it would have been misleading to exclude those cases.

In none of our patients were we able to make a diagnosis based upon response to treatment. Out of a total of 23 eyes, Acanthamoeba was identified by culture of corneal epithelium in 13, by histology in another, and by culture of corneal scrapes or storage cases (which, in combination with typical clinical features, is sufficient to make the diagnosis) in four. In the five eyes negative for culture and histology, there were clear clinical signs of Acanthamoeba keratitis as detailed in the paper. The rate of positive culture is similar to that of the largest single centre series of cases published to date. Response to treatment is not in itself a diagnostic criteria, but in the event of failure to respond, reassessment would be called for.

We restricted the discussion of laboratory diagnosis to culture on E coli seeded non-nutrient agar since this is the most widely employed technique and is suitable for use by hospital microbiologists without the need to set up a new and expensive field. With reference to the use of microscopy for early diagnosis, our own experience has been that it can be difficult to identify unstained amoebae in clinical specimens unless the patient is ophthalmologically seen within 48 hours of the initial diagnosis based upon microscopy should preferably be confirmed by culture. A simple method combining both approaches is to inoculate the sample directly into a 25 cm² dish containing 10 ml quarter strength Ringer's solution (concentration 3x10⁶/ml by optical density standards). Ameobae rapidly settle and adhere to the base of the flask, where they can be identified using an inverted phase contrast microscope. The initial impression can be confirmed by observation of multiplication of amoebae after 1-3 days of culture in air at 33°C.

The development of intolerance to drops in one patient in our series was probably related to the known epithelial toxicity of propamidine. The formulation of PHMB was identical to that used previously, and was of the same concentration (0.02%). The frequency of instillation is given in the methods section.

Lastly, treatment with chlorhexidine has been reported only very recently. The use of chlorhexidine may have an effect on the poor results of treatment with propamidine and other compounds. By March 1995 at least 184 eyes had been treated with PHMB in the UK alone (including those in our series). In these only five treatment failures occurred, and of these three were early cases where PHMB was used late in the disease process after unsuccessful use of propamidine. The use of chlorhexidine was considered during the search for an alternative effective antiprotozoal, and was rejected owing to a lower cytotoxic activity than PHMB and concerns about its toxicity. The theoretical merits of both compounds have been debated previously, but it should be noted that the results of the model chlorhexidine was toxic to endothelium at a concentration as low as 0.002%, while PHMB is relatively non-toxic. Additionally, chlorhexidine resistance appears to be common in Pseudomonas aeruginosa and has been reported in the known corneal pathogen Serratia marcescens. Bacterial co-isolates are commonly reported in Acanthamoeba keratitis, and it has been proposed that Acanthamoeba may gain access to the cornea only via an ocular infection by bacteria. It is also possible that secondary bacterial infection might arise in Acanthamoeba keratitis since chronic de-epithelialisation is common; this does not appear to occur in patients treated with PHMB. Chlorhexidine may well have a role to play in the treatment of Acanthamoeba keratitis, but the current situation is that while there have been many reports of successful use of PHMB in a large number of patients, this is not true of chlorhexidine.

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Further interest would include appropriate systemic methods which would make the diagnosis more reasonable, to the patient and to the physician. The conclusion, therefore, is based on an evidence-based medical opinion and would be difficult to change. The rationale for this is the absence of raised levels in all four forms of uveitis. The presence of raised levels in all forms of uveitis, including FHU, has been previously documented.

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Fuchs' heterochromic uveitis and sarcoidosis

EDITOR—Richard Goble and Philip Murray provided a further interest in the possible cause(s) of Fuchs' heterochromic uveitis (FHU), in reporting five patients with suggested sarcoidosis, including four with raised serum angiotensin converting enzyme (ACE). In patients with sarcoidosis, increased production of ACE is attributed to activated cells within granuloma. In 'granulomatous' uveitis it is reasonable, even in the absence of systemic symptoms, to investigate for the possibility of sarcoidosis. However, it is rarely appropriate to base the diagnosis on this for this purpose. We therefore rely on indirect methods of diagnosis.

Weinreb measured ACE levels in normal controls and found that 4.2% had significantly raised levels. By comparison, of those with 'granulomatous' uveitis but without evidence of systemic sarcoidosis, 44% had raised levels. His conclusion, that 'ocular sarcoidosis' may be diagnosed in the absence of systemic evidence, is, we feel, though unproved, and would explain a large subset of idiopathic uveitis. However, to extend this group to include forms of uveitis which are untypical of sarcoid related uveitis is mere speculation.

Weinreb's acknowledged feature of FHU, yet their appearance (small, dome-shaped, multiple, and translucent) and position (on the anterior iris surface, mostly peripupillary, scattered symmetrically) differentiate them from nodules seen in granulomatous disease (usually larger, fewer, often irregular in shape, sometimes buried within the stroma). Their presence in FHU cannot be missed because of a convincing case for a granuloma-like process. Ashour, though unsupported, and would explain a large subset of idiopathic uveitis. However, to extend this group to include forms of uveitis which are untypical of sarcoid related uveitis is mere speculation.

Weinreb's suggestion that the presence of raised serum angiotensin converting enzyme (ACE) levels is not specific for sarcoidosis is well illustrated in our patients. Five of five patients showed the characteristic clinical features of FHU. All patients had uniformly distributed, stellate keratic precipitates (KPs), iris stromal atrophy with heterochromia, and no posterior synechiae. Four out of five patients had iris nodules and three had posterior subcapsular cataract. Although mutton fat KPs are not a recognised feature of FHU, very occasionally these patients can develop a supra-achromatic anterior uveitis resulting in the formation of atypical KPs.

Sarcoidosis can be difficult to diagnose particularly in the absence of extraocular features. Although elevated angiotensin converting enzyme (ACE) levels are not specific for sarcoidosis the uveitis in these patients would be highly unlikely to result from any of the other causes of a raised ACE. In our case patient was Kveim positive and another had chest x-ray changes compatible with sarcoidosis.

We hope that a larger series of patients would be required in order to demonstrate any statistically significant association between raised ACE levels and FHU. Nevertheless, the finding of a sarcoid-like condition in five of five patients with Uveitis with serum angiotensin dependent condition forms only 3% of all uveitis entities would appear to be more than just coincidental.

Ocular sarcoidosis may not always present with the typical textbook findings, an example of this would be those patients who have a fundal appearance similar to birdshot retinochoroidopathy but are HLA-A29 negative. The features of FHU seen in our patients may be another atypical presentation.

Although FHU has been reported in combination with numerous conditions, a possible association with sarcoidosis has not been previously described. We felt that this was an interesting new finding which would support the theory that FHU may be a secondary phenomenon or a clinical end stage of a number of conditions.

Determining the importance of eye diseases in Africa

EDITOR.—In Africa the public health importance of trachoma and xerophthalmia is often underestimated when based on routine surveillance data and even data from population based surveys of low vision and blindness. Surveillance data may under-represent occurrence because both diseases are prevalent in children who rarely complain of it and health personnel select cases for examination even if they do not have an eye complaint. Population based surveys may under-represent occurrence if cluster sampling is used as this is a weak technique for detecting diseases with focal distribution. These problems are highlighted below using experiences in estimating the importance of these diseases in Ethiopia.

In 1978–80 the Ethiopian Nutrition Institute and the WHO conducted a nationwide assessment on the reporting of xerophthalmia in health centres and hospitals. The study concluded that the condition was rarely recorded. In the early 1980s two foci of vitamin A deficiencies were detected in famine-prone areas of the country. The prevalence of trachoma was estimated at 10-fold higher than previously suggested by hospital records. In 1981 a population based survey of blindness was undertaken. The survey found a blindness prevalence of between 1.35% and 1.5% and trachoma was found to be the major cause. However, the survey failed to detect a high prevalence of xerophthalmia in the country. By chance the xerophthalmia foci were not selected when the random sample of clusters were drawn.

Because of the limitation of the methods discussed above health authorities should identify areas where the population is likely to be at high risk, because of the presence of known risk factors for that condition, and then undertake a sample survey of the children within the high risk areas. This should provide a more realistic insight into the magnitude of the problem in specific high risk areas and direct planning for targeted intervention.

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