Prospective rather than retrospective studies are more likely to be published

During the past two decades the essentially anecdotal nature of medical practice has been largely replaced by “evidence based medicine.” Evidence based medicine incorporates the most reliable reproducible data from clinical studies, particularly clinical trials. Indeed, the multicentre, prospective, randomised clinical trial has become the gold standard by which other clinical data are now judged. The impact of this change on medical publications has been profound and cannot be over-emphasised. Prospective rather than retrospective studies are more likely to be published. Studies with inappropriate or no controls are often rejected outright. Appropriate use of statistics is now essential for publication of even the most straightforward clinical study. All of these changes are appropriate and make it more likely that data published today will still be useful in the future. On the other hand, do we really believe that no useful data can be obtained from a thoughtful small case series or even from the lowly case report?

In this issue of the BJO we introduce a new feature entitled “Hypothesis.” This feature will not be published in every issue of the journal, and we will not solicit papers for it. However, when one of the editors identifies a paper that raises what appear to be important clinical issues (we will not include any laboratory science studies) but does not contain all the necessary data to address the issues we will consider publishing the paper in this series. We will do so only after obtaining specific permission from the authors to publish it under this banner. We recognise that some authors may not want their work published in this format. Lambert and coworkers have agreed to have their paper “Weaning children with accommodative esotropia out of spectacles” (p 4) initiate the series. What are the important clinical questions raised by the authors and why might we not publish it under one of our usual headings?

Accommodative esotropia is usually divided into two distinct subtypes. One type results from an anomalous relation between the central innervational controls of accommodation and convergence in the presence of a modest need for accommodation (high AC/A ratio type). The second type occurs when there is a normal linkage of these functions that is overstressed by excessive demand (high hyperopia type). Both types of accommodative esotropia are treated by discouraging the accommodative innervational effort by providing the patient, at least initially, with their full cycloplegic hyperopic correction. The goal of the treatment is to reduce the esotropia to within 8 prism dioptres or less. This angle allows the development of at least peripheral fusion and probably an increase in fusional amplitudes. The usual practice is to only reduce the hyperopic correction as the patient’s refractive error becomes less with age. Raab and Spierrer have reported, therefore, that the majority of their adolescent patients still require a spectacle correction to control their accommodative esotropia. Are there any risks in continuing this usual practice pattern?

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There is now convincing evidence that infant rhesus monkeys who wear plus lenses become more hyperopic as the result of doing so. In other words, providing the full hyperopic refractive error in a spectacle correction to an infant rhesus monkey interferes with the normal emmetropisation process whereby young animals normally become less hyperopic as they become older. Even before these experimental studies had been published Repka et al had warned that prescribing the full cycloplegic hyperopic correction in children with accommodative esotropia might result in a similar interference with normal emmetropisation. Therefore, it seems there is good reason to study whether some or all accommodative esotropes can be weaned aggressively from their hyperopic spectacles without compromising the management of their strabismus and related amblyopia.

Lambert and coworkers have studied a very small group of accommodative esotropes where they attempted to do just that. The study is retrospective and with historical controls only. The study population may not be representative of a large unselected accommodative esotropia population. The authors describe their study group 1 (six patients) as not being high hyperopes (range +1.75 to +2.50 dioptres) and yet only one of the patients had a high AC/A ratio. Moreover, their study groups included only patients who were orthotropic while wearing their hyperopic spectacles. Yet, we know that a significant number of accommodative esotropes will obtain peripheral fusion only with their spectacle correction and not foveal fusion. Despite these shortcomings the findings of this study are thought provoking.

All of the patients in the authors’ study group 1 were weaned out of their spectacles successfully without compromising ocular motor alignment. Weaning was commenced at a median age of 6.3 years and completed by median age of 9.0 years. In their not precisely comparable historical control group all three patients remained in hyperopic corrections (final correction +2.75 to +4.50 dioptres). In contrast, in the group (group 1) that was weaned from spectacles the peak refractive error was +3.25 dioptres and the final refractive error at the time of spectacle discontinuation was +1.56 dioptres (range 0.0 to +3.06 dioptres). All four children in group 2 who could not be weaned from their spectacles had a normal AC/A ratio but their baseline hyperopia was +4.50 dioptres (range +3.00 to +5.00 dioptres). This would seem to confirm a generally held clinical opinion that high hyperopic accommodative esotropes are not likely ever to be weaned from their spectacle correction. This may be due to the fact that they do not seem to “lose” their hyperopia as they get older. In this group the hyperopia peaked at +5.55 dioptres and at the completion of the study had only decreased to +5.05 dioptres.

The major difference between groups 1 and 2 in the study by Lambert and coworkers is that the hyperopic refractive error in group 1 fell within the normal range for non-strabismic children of a similar age. In contrast, group 2 consisted entirely of “high” hyperopes. I would again emphasise that conspicuous by its relative absence is a study group of patients with a high AC/A ratio but with “normal” levels of hyperopia for their age. Most large studies of accommodative esotropia document that patients with these clinical features constitute at least 50% or more of all patients with accommodative esotropia. Only one of the 10 patients studied by Lambert and coworkers exhibited a high AC/A ratio.

The authors recognise and discuss their study’s limitations with its “selection bias,” “small number of children,”
neuropathy

Votruba and colleagues in this issue of Br J Ophthalmol describe crescents on the temporal portion of peripapillary atrophy, and unusual grey glaucoma. Optic nerve cupping is the single most important differentiating feature, being 94% specific for non-glaucomatous optic neuropathy with other optic neuropathies the presence of pallor extending beyond the area of cupping. While paracentral visual field loss is not uncommon in NTG, true central loss is unusual. These patients also demonstrated more visual acuity and visual field loss than would be expected from glaucoma with the same degree of optic nerve head cupping. While there can be a family history in NTG it is rare to find autosomal dominant pedigrees with multiple affected individuals. One might find pedigrees with a mixture of POAG and NTG patients. However, a pure NTG pedigree, like the one Bennett and colleagues described, is very rare. Patients with ADOA might, however, be mistakenly diagnosed with normal tension glaucoma (NTG).

Perhaps as important as the impact of these genetic studies on ADOA is the potential impact on understanding glaucoma. Fournier and colleagues described nine patients who had been originally diagnosed with NTG, but were eventually found to have ADOA. A large cup to disc ratio was found in at least one eye of eight (89%) of these patients. Patients who had peripapillary atrophy and all nine had grey crescents. Aung and colleagues found no increase in OPA1 mutations among POAG patients compared with control individuals. The found OPA1 intervening sequence polymorphisms in 20% of NTG patients compared with only 3.7% of normal control subjects.

Are there large numbers of patients with ADOA who have been misdiagnosed as having NTG? Probably not. Besides the similarities between ADOA and NTG, Votruba and associates catalogue the features of ADOA that should help to differentiate these patients from those with NTG. Unlike NTG, their ADOA patients had a very early age of onset (the mean onset of symptoms was at age 7 years and was never later than age 25 years). Their patients also demonstrated predominantly central visual field loss with relative peripheral visual field sparing. While paracentral visual field loss is not uncommon in NTG, true central loss is unusual. These patients also demonstrated more visual acuity and visual field loss than would be expected from glaucoma with the same degree of optic nerve head cupping. While there can be a family history in NTG it is rare to find autosomal dominant pedigrees with multiple affected individuals. One might find pedigrees with a mixture of POAG and NTG patients. However, a pure NTG pedigree, like the one Bennett and colleagues described, is very rare. Patients with ADOA always demonstrate pallor extending beyond the area of cupping. In studies comparing glaucomatous optic neuropathy with other optic neuropathies the presence of pallor was the single most important differentiating feature, being 94% specific for non-glaucomatous optic neuropathies.

Autosomal dominant optic atrophy is an important, but rare, disease. Perhaps as important as the impact of these genetic studies on ADOA is the potential impact on understanding a disease that more commonly leads to retinal ganglion cell death, optic nerve head cupping, and loss of visual function—glaucoma.

Optic neuropathy

The OPA1 gene and optic neuropathy

W L M Alward

Each genetic discovery will help to solve a small piece of the puzzle of optic nerve death

The optic nerve head findings in autosomal dominant optic neuropathy (ADOA) are well described in the literature. These patients demonstrate optic nerve head pallor, cupping, peripapillary atrophy, and unusual grey crescents on the temporal portion of their optic nerve heads. The report by Votruba and colleagues in this issue of the BJO (p 48) improves upon previous descriptions of the optic nerve in ADOA because it includes only patients with genetic confirmation of the diagnosis. All patients had either a mutation in the OPA1 gene or demonstrated linkage in their family to chromosome 3q28-qter. Previous reports used only clinical features to diagnose ADOA and may have included patients with optic atrophy due to other disorders.

Votruba and associates evaluated the optic nerves of 29 patients from 12 pedigrees. Pallor, either temporal or diffuse, was present in all eyes. An enlarged cup to disc ratio (>0.5) was found in 48% of eyes and deep excavation was found in 21% of eyes. Peripapillary atrophy was seen in 69% of eyes and a temporal grey crescent in 31%.

With the exception of pallor, these optic nerve changes are all also seen in glaucoma. Optic nerve cupping is the defining feature of all forms of glaucoma. Peripapillary atrophy is common in glaucoma and can increase as the glaucoma worsens. The grey crescent on the temporal optic nerve head noted by Votruba et al was first described by Shields among African-American patients with primary open angle glaucoma (POAG). There are also histopathological similarities between ADOA and glaucoma. Like glaucoma, ADOA is characterised by retinal ganglion cell degeneration with atrophy of the optic nerve. Because ADOA eyes typically have normal intraocular pressures (IOP) they would probably not be confused with high pressure POAG. In fact, a study of POAG patients found no increase in prevalence of OPA1 gene sequence variations when compared to normal control subjects. Patients with ADOA might, however, be mistakenly diagnosed with normal tension glaucoma (NTG).

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Glaucoma has been a difficult disease to study molecularly. Linkage studies on POAG and NTG families are hampered by the late onsets of these diseases. Even when there is a strong family history, the parents of the affected proband and some siblings are probably deceased at the time of family study. The children may be too young to be affected. These problems make the acquisition of the large pedigrees needed for linkage studies difficult. To circumvent this problem researchers have used early onset diseases as models for similar late onset diseases. For POAG the study of autosomal dominant juvenile onset open angle glaucoma led to linkage of the disease to chromosome 1q\textsuperscript{10} and ultimately to the discovery of the gene myocilin.\textsuperscript{11} Myocilin, besides causing most cases of autosomal dominant juvenile onset open angle glaucoma, was also found to cause about 3–5% of the more common adult onset POAG.\textsuperscript{11} 12 Like myocilin, it may be that some mutations in \textit{OPA1} cause early onset severe disease while other mutations cause late onset mild disease that is difficult to distinguish from NTG.\textsuperscript{1} 12 With further research we may find that \textit{OPA1} and genes that interact with \textit{OPA1} are involved in a variety of optic neuropathies. Each of these genetic discoveries will help to solve a small piece of the puzzle of optic nerve death.

\textbf{REFERENCES}