Retinopathy of prematurity

ROP and neurodevelopmental disabilities

G E Quinn

The dilemma in premature babies

There are essentially three ways in which blindness from retinopathy of prematurity (ROP) can be prevented, including elimination of premature birth, changes in neonatal care, and improved detection and treatment of established eye threatening retinopathy. It is on the latter that the attention and efforts of the ophthalmic community have been focused, leaving the first two to the paediatricians, perinatologists, neonatologists, nurses, and others who care for these tiny babies. What Darlow et al have done in the paper in this issue of the BJO (p 1592) is direct our attention to the second possibility—that is, neonatal care may be able to be altered to decrease the incidence of potentially blinding disease.

Darlow et al document a remarkable variability in the prevalence of severe ROP among the nurseries in the neonatal intensive care units in the Australian and New Zealand Neonatal Network. This variability is generally expected when morbidity or mortality results are compared across centres, even in an essentially population based study that this report represents (the four tertiary paediatric care referral centres are excluded from the analysis reported by Darlow et al). The variability in such reports can usually be explained by a combination of several factors, including case mix, assessment of the primary outcome measure, viability considerations by neonatologists at the various centres, and variations in clinical practice. For example, the percentage of high risk deliveries may differ dramatically among nurseries, leading to more at-risk infants in one nursery than another. Smaller nurseries may also have greater variation in the incidence of severe ROP because of sampling variability. In addition, standardisation of outcome measures in multicentre studies represents a huge challenge and can seriously impact the perceived prevalence of severe disease.

Thanks to a large enough sample and novel analytical techniques, Darlow et al have been able to take into account many of the potential confounding variables using logistic regression models. They find that variability across nurseries in the rates of severe ROP requiring treatment is not explained by case mix, sampling, or outcome assessment, but rather is probably the result of clinical practice in the individual nurseries. In their analysis, they wisely chose to highlight the improvement in rates of serious ROP that could be reached if clinical practice was altered to achieve the “best practice” rates achieved in the top 20th percentile of the nurseries, rather than focusing on the “problem” nurseries. Using this systematic approach to changes in clinical care would lower the rate of severe ROP to 5.9% in the top 20% of nurseries from the overall rate of 9.6%. They estimate that 79 cases of severe ROP would have been prevented.

A major problem that arises when practice patterns are changed is that interventions aimed at decreasing the rate of one serious problem may increase the rate of another, equally serious problem. A very clearcut example of this was provided in the 1950s when oxygen was found to be the cause of blinding ROP and its delivery markedly restricted.1 This led to an increase in mortality and spastic diplegia among premature babies,2 and it was estimated that 16 infants died from curtailed oxygenation for each case of blindness prevented.3 This observation has particular clinical relevance when evaluating possible changes in clinical care of premature babies, a population that has had an increased survival rate as a result of advances in perinatal and neonatal medicine over the past 20 years in countries with high levels of human development; it is also a population in which we have only an evolving understanding of the developmental disabilities that are detected later in life.4-6 Since clinical care of the premature baby is directed broadly at prevention of illness, undernutrition, and infection during a time of rapid brain growth and development, it is not hard to postulate that systemwide changes in practice may differentially impact on the occurrence of cerebral palsy, visual and hearing impairments, behavioural and social problems, and learning difficulties.7 When considering changes in practice patterns, clearly the possible effect of any change must concentrate not only on survival, but also on lifelong disabilities that may occur in this vulnerable population.

Identifying and implementing practice pattern changes may decrease the prevalence of severe ROP and, with appropriate treatment, of blindness. However, most children being blinded from ROP do not live in countries with high levels of human development, but rather they are born in countries with middle levels of human development, where neonatal services are rapidly expanding and where limited resources may severely impact delivery of the highest levels of neonatal care.8 Thus, the alterations in clinical practice that may arise from examining the “best practice” nurseries in Australia and New Zealand may have limited generalisability to the nurseries that care for the largest proportion of babies at risk of blindness because of severe ROP.

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Deep lamellar keratoplasty (DLK) is a logical step in the surgical management of corneal stromal opacification in the setting of functional endothelium. In DLK, pathological stroma is excised down to Descemet’s membrane, and offers the promise of better visual outcomes compared with conventional lamellar grafting. Since this procedure was first reported by Arichila in 1985, several large case series have described favourable visual results after DLK. A report of 120 cases by Sugita and Kondo demonstrated that corrected visual acuity improved by 0.09 to 0.6 on average after DLK. Anwar and Teichmann reported that 89% of 181 eyes treated by DLK achieved visual acuity of 20/40 or better. More recently, Shimazaki and associates performed a randomised prospective trial of DLK versus penetrating keratoplasty, showing that visual function after DLK, as measured by corrected visual acuity, contrast visual acuity, the glare test, and corneal topography, was comparable to that achieved in penetrating keratoplasty. It should be noted that DLK was superior to penetrating keratoplasty in measures of operative morbidity such as continuous endothelial cell loss and intraocular complications. These results suggest that DLK is a safe alternative to penetrating keratoplasty in eyes without endothelial abnormalities. These promising findings regarding DLK underscore the importance of overcoming technical challenges such as achieving thorough stromal tissue excision without perforation of Descemet’s membrane.

Deep lamellar keratoplasty is a logical step in the surgical management of corneal stromal opacification in the setting of functional endothelium. Most corneal surgeons have confronted the technical challenge of deep lamellar dissection and the attendant risk of puncturing Descemet’s membrane during DLK. To facilitate the dissection of stromal tissue while reducing the risk of perforation, Arichila and Price employed an air injection technique to separate tissue planes. Sugita and associates used a hyaluronic acid for viscoelastic injection to dissect Descemet’s membrane from the stromal tissue, leaving the healthy portion of the host cornea intact. DLK is donor tissue, leaving the healthy portion of the host cornea intact. DLK is donor tissue, leaving the healthy portion of the host cornea intact.

With continued improvements in surgical technique it may become the procedure of choice for keratoplasty in most eyes without endothelial abnormalities.

Overcoming the technical challenges of deep lamellar keratoplasty

M Yamada
Age related macular degeneration

Mouse models may provide new insight into the relation between cholesterol and age related macular degeneration

J L Duncan

With the goal of preventing vision loss from this disease, it is important to identify modifiable risk factors that may be targets for intervention

Age related macular degeneration (AMD) is the leading cause of severe vision loss among the elderly in the United States, Europe, and Australia. However, the cause of this blinding disease remains a topic of active investigation. Most agree the pathogenesis of AMD is multifactorial and that it results from the interaction of genetic, environmental and ageing effects. Evidence from population based studies has supported a role for heredity in the pathogenesis of AMD. Recent studies have identified a polymorphism in the gene for complement factor H which may be present in up to half of all white AMD patients. However, polymorphisms in this gene are also frequently found in Japanese and Chinese populations, where AMD infrequently causes vision loss. Clearly, development of AMD depends on the interaction of genetic background with other, presumably environmental, factors.

With the goal of preventing vision loss from this disease, it is important to identify modifiable risk factors that may be targets for intervention. Some, but not all, epidemiological studies have identified an association between cardiovascular disease risk and AMD. Cigarette smoking, a well recognized risk factor for cardiovascular disease, is the most consistently demonstrated modifiable risk factor contributing to AMD, and its role in complement activation has been considered supportive evidence of the part played by complement factor H mutations. Recent case-control and prospective studies have identified elevated C reactive protein, an inflammatory biomarker associated with cardiovascular disease, as a risk factor for AMD and AMD progression. Systemic hypertension has been associated with neovascular AMD and a poorer response to laser therapy for choroidal neovascularisation (CNV) in patients with AMD. Some studies have found an association between markers of systemic atherosclerosis and AMD, but other large population based studies have found no consistent association. Increased dietary consumption of saturated fat, monounsaturated and polyunsaturated fat and vegetable fat has been associated with early and late AMD in various studies. Some recent studies have identified an association between use of cholesterol lowering medications, such as statins, and reduced risk of early or late AMD, while others have found no such association. Although total serum cholesterol has been associated with neovascular AMD in a large case-control study, many large population based studies have found no association. Some studies have suggested an association between different lipoprotein polymorphisms and risk of AMD, including apoE, apo B, and apo A1. Certainly the relation between cardiovascular risk factors, lipid metabolism, and AMD remains confusing.

The findings described in LDL receptor deficient mice may provide insight into the mechanism of early AMD

Insight into the role lipid metabolism has in the development of early AMD has come from the study of preclinical models. Although no murine model exists that exactly replicates the phenotype seen in human AMD, studies have shown that C57BL/6 mice fed a high fat diet and briefly exposed to blue-green light develop basal laminar deposits, a histological feature of human eyes with AMD. Mice with null mutations in apoE have shown basal linear deposits and thickened Bruch’s membranes, similar to findings in human eyes with AMD. However, neither of these models develops choroidal neovascularisation or geographic atrophy, the stages
of AMD associated with vision loss in patients, limiting our understanding of the mechanisms responsible for these sight-threatening complications. In this issue of the BJO (p 1627), Rudolf and colleagues present novel information about mice with a null mutation for the low density lipoprotein (LDL) receptor, which have been studied as a murine model of atherosclerosis. After receiving a high fat diet, LDL receptor deficient mice develop membrane bound translucent particles within a significantly thickened Bruch’s membrane, while control mice with normal LDL receptors show no Bruch’s membrane abnormalities. The membrane bound translucent particles observed in the LDL receptor deficient mice resemble vesicles observed in histological sections of basal linear deposits and large drusen, findings specific for early AMD. Although plasma cholesterol is significantly elevated in LDL receptor deficient mice fed both normal and high fat diets, it is not clear from the present work that the changes in Bruch’s membrane in LDL receptor deficient mice derive from plasma cholesterol rather than from an intracellular source. Further ultrastructural analysis of the lipid composition of Bruch’s membrane in LDL receptor deficient mice, using previously described methods to preserve neutral lipids, may provide insight into whether these deposits result from elevated plasma lipid levels or an intracellular source. Such information may clarify the discrepancies noted between plasma lipid abnormalities and risk of AMD in epidemiological studies.

Of interest, the authors demonstrate immunohistochemical reactivity for vascular endothelial growth factor (VEGF) in the basal retinal pigment epithelial (RPE) cells, the outer plexiform layer, and the photoreceptor inner segments of LDL receptor deficient mice, which increased after the mice received a high fat diet. The authors state that no spontaneous CNV was observed in the mice studied despite high levels of VEGF expression. However, the mice in this study were investigated at 4 months of age. It will be interesting to observe LDL receptor deficient mice at senescent ages to determine if the changes described in Bruch’s membrane progress with advanced age or are accompanied by the development of CNV or RPE atrophy. Other mutant mice with phenotypes similar to human AMD develop fundus and histological changes only after the age of 9 months, with geographic atrophy and CNV developing only after 16 months and 18 months of age, respectively.

Even in the absence of correlates of late AMD, the findings described in LDL receptor deficient mice may provide insight into the mechanism of early AMD. The fact that the mice develop abnormally thickened Bruch’s membranes, similar to early AMD, and demonstrate VEGF upregulation suggests that ischaemia or oxidative stress occurs even in early stages of AMD, perhaps as a result of compromised diffusion from the choriocapillaris to the outer retina. LDL receptor deficient mice will provide a useful model of early AMD and may allow investigators to determine the part abnormalities of cholesterol metabolism may play in its pathogenesis. Whether or not deficiencies in the LDL receptor are associated with AMD in humans, the ocular phenotype of LDL receptor deficient mice described in the present work should encourage investigators to study murine models of atherosclerosis with careful attention to the eyes.

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