BJO

British Journal of Ophthalmology

Editorials

Is botulinum toxin helpful in squint management?

The first report of the experimental use of botulinum toxin relevant to ophthalmologists was published from Alan Scott's laboratory in 1973, and concerned the creation of incomitant strabismus in rhesus monkeys by injection and paralysis of the medial rectus muscle.[1] With the optimal dosage of botulinum toxin A, when the paralysis resolved a concomitant exodeviation persisted and it appeared that in these animals the agonist:antagonist muscle balance had been altered permanently. On this basis the technique appeared to be a possible alternative to strabismus surgery. The initial publications on the effect of botulinum toxin injection on concomitant strabismus in adults were open non-comparative studies, but appeared to substantiate the hypothesis that a permanent realignment of the eyes could be achieved.[2] However, the strong tendency for recurrence of the deviation in the absence of sensory and motor binocularity before treatment was highlighted in later publications.[3] In a comparative trial of botulinum toxin injection versus surgery for the treatment of strabismus in adults without fusion, surgery gave considerably better results.[4] For many strabismus surgeons interest in botulinum toxin treatment as a directly comparable alternative to surgery waned.

There is less literature on the use of botulinum toxin in childhood strabismus; this is partly because the electromyography guided injection technique requires a local anaesthetic and is inapplicable under general anaesthesia.[5] The technique can be used with local anaesthetic and intravenous ketamine in children, but this agent frequently causes nightmares and hallucinations. Also, side effects of the botulinum toxin owing to spread to other extraocular muscles and the levator are commoner in children because of the small orbit. In the UK, ethics committees have refused consent to carry out comparative studies in patients with congenital esotropia which, because of the possibility of establishing some degree of binocularity, is arguably the group with the best potential for long term alignment. Moreover, many ophthalmologists feel intuitively that strabismus surgery is a better option in children.

Against this background the paper from Tejedor and Rodriguez (p 110) is an important contribution. In a group of children needing retreatment after previous surgery for acquired esotropia, there was no difference in the motor and sensory outcomes between those treated with botulinum toxin and those reoperated.

The importance of this paper is threefold. Firstly, it addresses a specifically defined management issue by randomly allocating one form of treatment or another. This approach is widely recognised to be the appropriate test of a novel treatment, but one that is rarely practised particularly in the surgical specialties. The precise role of botulinum toxin in strabismus management remains unclear to many ophthalmologists, because of the lack of clear guidelines that can only be developed from controlled studies such as this. Secondly, the paper demonstrates the usefulness of botulinum toxin in the defined clinical circumstances. The treatment was safe, as effective as surgery, and did not produce side effects (for example, vertical deviations) that might prejudice the long term outcome. Injection treatment is also repeatable, does not induce scar tissue, and does not preclude the possibility of further surgery at a later stage. Thirdly, the outcomes described suggest that there may be a difference in the potential for botulinum toxin treatment to alter long term ocular alignment in children as opposed to adults. This may be partly because the children treated in this study had some fusional potential, whereas many of the adults treated in other studies do not. It may also be that the structural changes in the extraocular muscles described after botulinum toxin injections have more impact in the child than in the adult and permanently alter the agonist:antagonist balance.[6]

As predicted by Scott in 1973 botulinum toxin treatment has proved to be highly effective for many forms of focal dystonia in which it is now the treatment of choice.[7] Its role in strabismus management is clear in muscle paresis and other situations where binocular potential is good.[8 9] More thoughtful well designed studies such as that of Tejedor and Rodriguez are still needed to clearly define its role in other situations.

JOHN ELSTON

Oxford Eye Hospital, Walton Street,
Oxford OX2 6HE

1 Scott AB, Rosenbaum AL, Collins CC. Pharmacologic weakening of extraocular muscles. *Invest Ophthalmol* 1973;**12**:924–7.
2 Scott AB. Botulinum injection into extraocular muscles as an alternative to strabismus surgery. *Ophthalmology* 1980;**87**:1044–9.
3 Elston JS, Lee JP, Powell CM, Hogg C, Clarke P. Treatment of strabismus in adults with botulinum toxin A. *Br J Ophthalmol* 1985;**69**:718–24.
4 Carruthers JDA, Kennedy RA, Bagaric D. Botulinum versus adjustable suture surgery in the treatment of horizontal misalignment in adult patients lacking fusion. *Arch Ophthalmol* 1990;**108**:1432–5.
5 Scott AB, Magoon EH, McNeer KW, Stager DR. Botulinum treatment of childhood strabismus. *Ophthalmology* 1990;**97**:1434–8.
6 Spencer RF, McNeer KW. Botulinum toxin paralysis of adult monkey extraocular muscle. *Arch Ophthalmol* 1987;**105**:1703–11.
7 Report of the Therapeutic and Technology Assessment Sub Committee of the American Academy of Neurology. The clinical usefulness of botulinum toxin A in treating neurologic disorders. *Neurology* 1990;**40**:1332–6.
8 Fitzsimons R, Lee JP, Elston JS. Treatment of sixth nerve palsy in adults with combined botulinum toxin chemodenovation and surgery. *Ophthalmology* 1988;**95**:1535–42.
9 Petitto VEB, Buckley EG. Use of botulinum toxin in strabismus after retinal detachment surgery. *Ophthalmology* 1991;**98**:509–13.

Growth factors in proliferative vitreoretinopathy

Surgical repair of retinal detachment complicated by proliferative vitreoretinopathy (PVR) remains complex and time consuming. Visual results of such surgery are frequently disappointing. Dissecting the network of growth factors/cytokines involved in PVR is a comparable challenge which may eventually result in improved anatomical and visual outcomes.

Several lines of evidence point to a role for soluble mediators ("growth factors") in the process of periretinal membrane formation seen in PVR. Firstly, studies of cellular healing responses in other tissues have demonstrated a role for a number of growth factors (sometimes termed "fibrogenic cytokines") in mediating cellular chemotaxis and proliferation, neovascularisation, extracellular matrix production, wound remodelling, and contraction, processes essential to the normal wound healing response.[1 2] Secondly, several in vitro investigations have demonstrated that retinal pigment epithelium and retinal glia are responsive to a number of growth factors.[3–6] The in vitro retinal pigment epithelium mediated contraction of collagen gels has also been shown to be growth factor dependent.[7 8] Thirdly, analysis of specimens from eyes with PVR[9] reveals the presence of elevated growth factor levels in vitreous[10–13] and growth factor deposition in epiretinal membranes.[14–19] Cells in PVR epiretinal membranes have also been shown to express growth factor mRNA[20] which together with in vitro work on retinal pigment epithelium secretion of growth factors[4 21–23] suggests that there may be local growth factor production within PVR epiretinal membranes and a potential autocrine action on retinal pigment epithelium function. Lastly, experimental studies have demonstrated the induction of a PVR-like response by intraocular injection of platelet derived growth factor (PDGF).[24]

The paper by Cassidy and co-workers in this issue of *BJO* (p 181) adds useful new information to the growing literature on growth factor involvement in PVR. Their essential finding is that levels of both PDGF and basic fibroblast growth factor (bFGF) are significantly raised in the vitreous of eyes with retinal detachment and PVR but not in eyes with retinal detachment without PVR. Both growth factors are known to be involved in the upregulation of wound healing[1 2] and the findings support previous observations that PDGF protein and its receptor are present on PVR epiretinal membranes[16] and in vitro work suggesting a role for PDGF and bFGF in PVR.[3 5 22] An association between raised PDGF levels and vitreous haemorrhage was also documented. Vitreous haemorrhage is considered a risk factor for PVR[25] although in this context it may in fact simply serve as a marker for blood-retinal barrier breakdown. The trend towards higher levels of PDGF in grade A PVR is also of interest, suggesting differing growth factors may be active at the various stages of progression of the process of membrane formation. Further work is necessary to clarify this point.

As knowledge of the involvement of growth factors in PVR expands, additional questions are raised. The relative contributions of individual "fibrogenic" (for example, PDGF, bFGF, transforming growth factor β) and "inflammatory" (for example, interleukins 1 and 6, tumour necrosis factor α) growth factors are unknown and potentially single growth factors may hold the key to the PVR process. It is uncertain whether the growth factor profile in PVR represents a qualitative or quantitative difference from that of the processes of retinal repair seen in uncomplicated retinal reattachment. As manipulation of growth factor responses becomes a clinical reality a fundamental issue is to determine if specific targeting of growth factors can provide a means of treating and/or preventing PVR. Until effective adjunctive treatment is available for PVR the single option of vitreoretinal surgeons will continue to be direct surgical relief of vitreoretinal traction and retinal foreshortening.

DAVID G CHARTERIS

Vitreoretinal Unit,
Moorfields Eye Hospital,
City Road,
London EC1V 2PD

1 Bennett NT, Schultz GS. Growth factors and wound healing: biochemical properties of growth factors and their receptors. *Am J Surg* 1993;**165**:728–37.
2 Bennett NT, Schultz GS. Growth factors and wound healing: part II Role in normal and chronic wound healing. *Am J Surg* 1993;**166**:74–81.
3 Campochiaro PA, Glaser BA. Platelet derived growth factor is chemotactic for human retinal pigment epithelial cells. *Arch Ophthalmol* 1985;**103**:576–9.
4 Burke JM. Cell interactions in proliferative vitreoretinopathy: do growth factors play a role? In: Heimann K, Wiedemann P, eds. *Proliferative vitreoretinopathy*. Heidelberg: Kaden, 1989:80–7.
5 Leschey KH, Hackett SF, Singer JH, Campochiaro PA. Growth factor responsiveness of human retinal pigment epithelial cells. *Invest Ophthalmol Vis Sci* 1990;**31**:839–46.
6 Harvey AK, Roberge F, Hjelmeland LM. Chemotaxis of rat retinal glia to growth factors found in repairing wounds. *Invest Ophthalmol Vis Sci* 1987; **28**:1092–9.
7 Pena RA, Jerdan JA, Glaser BM. Effects of TGF-beta and TGF-beta neutralizing antibodies on fibroblast-induced collagen gel contraction: implications for proliferative vitreoretinopathy. *Invest Ophthalmol Vis Sci* 1994;**35**:2804–8.
8 Hunt RC, Pakalnis VA, Choudhury P, Black EP. Cytokines and serum cause α2b1 integrin-mediated contraction of collagen gels by cultured retinal pigment epithelial cells. *Invest Ophthalmol Vis Sci* 1994;**35**:955–63.
9 Charteris DG. Proliferative vitreoretinopathy: pathobiology, surgical management, and adjunctive treatment. *Br J Ophthalmol* 1995;**79**:953–60.
10 Grisanti S, Wiedemann P, Weller M, Heimann K, Zilles K. The significance of complement in proliferative vitreoretinopathy. *Invest Ophthalmol Vis Sci* 1991;**32**:2711–7.
11 Glaser BM, Connor TB, Roberts AB, *et al*. Correlation of fibrosis and transforming growth factor-beta type 2 levels in the eye. In: Heimann K, Weidemann P, eds. *Proliferative vitreoretinopathy.* Heidelberg: Kaden, 1989:120–7.
12 Gaudric A, Glacet-Bernard A, Falquerho L, Barritault D, Coscas G. Transforming growth factor beta in vitreous from patients with epiretinal proliferation. In: Heimann K, Weidemann P, eds. *Proliferative vitreoretinopathy*. Heidelberg: Kaden, 1989:118–9.
13 Kauffmann DJH, van Meurs JC, Mertens DAE, *et al*. Cytokines in vitreous humor: interleukin-6 is elevated in proliferative vitreoretinopathy. *Invest Ophthalmol Vis Sci* 1994;**35**:900–6.
14 Fredj-Reygrobellet D, Baudouin C, Negre F, *et al*. Acidic FGF and other growth factors in preretinal membranes from patients with diabetic retinopathy and proliferative vitreoretinopathy. *Ophthalmic Res* 1991;**23**: 154–61.
15 Malecaze F, Mathis A, Arne JL, *et al*. Localisation of acidic fibroblast growth factor in proliferative vitreoretinopathy membranes. *Curr Eye Res* 1991;**10**: 719–29.
16 Robbins SG, Mixon RN, Wilson DJ, *et al*. Platelet-derived growth factor ligands and receptors immunolocalised in proliferative retinal diseases. *Invest Ophthalmol Vis Sci* 1994;**35**:3649–63.
17 Baudouin C, Philip PJM, Brignole F, *et al.* Immunolocalisation of interferon gamma in proliferative preretinal tissues. *Invest Ophthalmol Vis Sci (Suppl)* 1993;**34**:951.
18 Limb GA, Alam A, Earley O, *et al.* Distribution of cytokine proteins within epiretinal membranes in proliferative vitreoretinopathy. *Curr Eye Res* 1994; **13**:791–8.
19 Vinores SA, Henderer JD, Mahlow J, *et al*. Isoforms of platelet-derived growth factor and its receptors in epiretinal membranes: immunolocalisation to retinal pigment epithelial cells. *Exp Eye Res* 1995;**60**:607–19.
20 Limb GA, Earley O, Jones SE, *et al*. Expression of mRNA coding for TNFα, IL1b, and IL6 by cells infiltrating retinal membranes. *Graefes Arch Clin Exp Ophthalmol* 1994;**232**:646–51.
21 Jaffe GJ, Van Le L, Valea F, *et al*. Expression of interleukin-1 alpha, interleukin-1 beta, and an interleukin-1 receptor antagonist in human retinal pigment epithelial cells. *Exp Eye Res* 1992;**55**:325–35.
22 Campochiaro PA, Hackett SF, Vinores SA, *et al.* Platelet-derived growth factor is an autocrine growth stimulator in retinal pigment epithelial cells. *J Cell Sci* 1994;**107**:2459–69.
23 Tanihara H, Yoshida M, Matsumoto M, Yoshimura N. Identification of transforming growth factor beta expressed in cultured human retinal pigment epithelial cells. *Invest Ophthalmol Vis Sci* 1993;**34**:413–9.
24 Yeo JH, Sadeghi J, Campochiaro PA, Green WR, Glaser BM. Intravitreous fibronectin and platelet-derived growth factor. A new model for traction retinal detachment. *Arch Ophthalmol* 1986;**104**:417–21.
25 Campochiaro PA. Pathogenic mechanisms in proliferative vitreoretinopathy. *Arch Ophthalmol* 1997;**115**:237–41.