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Proliferative vitreoretinopathy—developments in adjunctive treatment and retinal pathology

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Abstract

Proliferative vitreoretinopathy (PVR) remains a difficult management problem despite advances in vitreoretinal surgery. There is still a significant incidence of PVR in rhegmatogenous retinal detachment and other forms of retinal disease. Surgery for PVR now has a high anatomical success rate although visual results are often disappointing. The use of adjunctive treatments to prevent cellular proliferation holds promise for the prevention of PVR or recurrences after surgery. Control of proliferation and strategies aimed at improving visual outcome are important areas of future research in PVR and other forms of retinal disease. Studies of the intraretinal and peri-retinal pathology of PVR have demonstrated characteristic changes which may have a significant influence on visual outcome and surgical management.
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Introduction

Incidence

Proliferative vitreoretinopathy (PVR) is generally held to have an incidence of 5–10% of all rhegmatogenous retinal detachments.[1] This figure derives from published data prior to the early 1980s and would result in 300–600 cases per year in the United Kingdom. Over the last 20 years vitreoretinal surgical techniques have evolved, a greater emphasis has been placed on success in primary retinal detachment surgery to prevent PVR, case selection has been refined and it might be expected that the incidence of PVR would decline. A survey of published series through the 1990s to date suggests, however, that the frequency of the condition remains largely unchanged in primary retinal detachment, with incidences ranging from 5.1–11.7%.[2–8] These series reflect the changing case mix seen in primary retinal detachment surgery, for example increasing numbers of pseudophakic retinal detachments[2,4] and also the evolution of surgical techniques including primary vitrectomy.[6] Overall these data suggest that there remains a significant incidence of PVR following primary retinal detachment.

PVR continues to have a higher incidence in other vitreoretinal conditions. For example in giant retinal tears (which are often excluded from series of primary retinal detachment), the incidence varies from 16–41% in recent series.[9–13] In penetrating ocular trauma the underlying pathophysiology of PVR is modified by additional factors such as the presence of uveitis and a greater degree of blood–ocular barrier breakdown and vitreous haemorrhage. Exogenous cell types may also be present, for example episcleral fibroblasts introduced at the time of the penetrating injury. In penetrating trauma PVR is estimated to occur in between 10 and 45%[14–25] of eyes with a mean incidence of approximately 25%.

PVR has become an important complication in retinal translocation surgery. Incidences of 18–23% have been reported where a 360 degree retinotomy has been undertaken to allow maximum foveal translocation (Claes C, Bartz-Schmidt K, Eckardt C. Advanced Vitreoretinal Course, Antwerp, Belgium 16–18 March 2001). The frequency of PVR appears to be lower where an extensive retinotomy is not performed.[26]

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Outcomes

Surgical success rates have improved significantly since initial studies on the management of PVR by vitrectomy. Lewis, Aaberg and Abrams have reported final posterior re-attachment rates of 90% for initial surgery for PVR and 86% for repeat surgery.[27,28] In the Silicone Study there was a final posterior re-attachment rate of 77% for cases managed with silicone oil and 79% for those treated with C3F8 gas tamponade.[29,30] Visual results from these studies are less satisfactory. In the Lewis, Aaberg and Abrams series, 19% of eyes undergoing initial vitreoretinal surgery for PVR achieved 20/100 or better vision and only 11% of repeat surgery eyes achieved this level. In the Silicone Study overall, 25% achieved 10/100 or greater vision.

The binocular visual outcome on these eyes is often equally unsatisfactory. A study by Andenmatten and Gonvers[31] analysed the results of 44 successfully treated PVR retinal detachments with healthy fellow eyes. They found that only 14 had some degree of stereoopsis and 15 had a manifest squint, 30 complained of photophobia, eight had diplopia and 20 closed their operated eye when performing manual tasks. Twenty-five of the 44 patients described their visual comfort as medium to bad.

Because of the often disappointing results of PVR surgery its justification has been questioned. Patients, however, often report that they considered the surgery had been worthwhile.[31,32] The status of the fellow eye in eyes having undergone surgery for PVR was analysed in a recent report by Schwartz and Kreiger.[33] They documented that over 50% of these eyes had vision threatening pathology and approximately 75% of these had had rhegmatogenous events (retinal tears or detachment). Forty-seven per cent of eyes with vision threatening pathology had a final visual acuity of 20/50 or worse and over half of these had a final visual acuity of 20/250 or less. Five per cent of the entire group ended with no light perception vision in the fellow eye. Given the uncertain visual prognosis in the fellow eye and patients reporting satisfaction with surgery, it appears that at present PVR surgery remains justified.

Challenges in PVR management

Control of the biological processes involved in proliferation and retinal wound healing would increase the success of not only primary retinal detachment repair and PVR surgery but also assist in the management of other forms of posterior segment disease such as ocular trauma and age-related macular degeneration. Primary prevention of PVR may in the future lie with the identification of high risk cases and secondary prevention strategies to control re-proliferation may involve approaches which differ to those used in primary prevention.

The poor visual outcome of many PVR cases requires further investigation to define both its causes and potential therapeutic measures.

Adjunctive treatment

A high success rate in primary retinal detachment surgery remains the basis for the prevention of PVR. In cases that develop PVR and in others identified initially as high risk the use of adjunctive medical agents is potentially of value in increasing surgical success rates.

Advances in the understanding of the pathobiology of PVR have led to identification of various components of the proliferative process which may be targeted in prevention strategies.[34–36] Adjunctive agents may specifically or non-specifically target: (a) the proliferating cell types known to be involved in PVR; (b) the production and subsequent contraction of the extracellular matrix; (c) the initial deposition of fibrin which may serve as the scaffold for subsequent membrane formation; and (d) the various growth factors which have been documented to mediate PVR development.[37] A number of agents have been analysed in experimental systems and in uncontrolled clinical trials (for a detailed discussion see Charteris[34]). The first reported randomised controlled trials on the use of adjunctive agents in the management of PVR was the European Daunorubicin trial co-ordinated by Wiedemann and colleagues.[38] This was a multicentre randomised controlled trial recruiting patients with established PVR. A 10-min infusion of Daunorubicin at the time of vitrectomy surgery was used in the treatment group. The study demonstrated a significant reduction in the number of re-operations within one year in the treatment group and was thus the first trial to demonstrate clinically a biological effect of adjunctive medication on the PVR disease process. The primary outcome measure, retinal re-attachment rate at 6 months, marginally failed to show a significant improvement in the treatment group.

In the United Kingdom a two centre study has investigated the use of a combination of 5-fluorouracil and low molecular weight heparin in the prevention of PVR.[39] High risk cases were selected on the basis of previous work which had analysed various risk factors known to be associated with PVR.[40,41] Cases were then allocated to a treatment group which received a one hour infusion of 5-fluorouracil 200 μg per ml and low molecular weight heparin 5 IU per ml or to a control

group receiving a placebo infusion. The treatment combination resulted in a significant reduction in the rate of postoperative PVR development. Primary retinal reattachment and the number of re-operations due to PVR showed trends towards improvement in the treatment group but did not reach statistical significance. There did not appear to be any treatment-related complications. Based on the evidence of this study the use of this adjunctive combination may now be considered in eyes thought to be at high risk of PVR development undergoing vitrectomy for retinal detachment repair. A study on the use of this combination in established PVR subsequently failed to show a treatment benefit (unpublished data), suggesting that differing adjunctive agents may be necessary depending on the clinical setting.

Further work is necessary to define optimal adjunctive strategies in the management of PVR and other posterior segment pathologies. Refinements in case selection will allow a more targeted approach in the use of adjuncts. Additional indications such as giant retinal tears and ocular trauma deserve investigation as do other adjunctive agents. Sustained delivery systems may be of considerable value in future treatment strategies particularly in the prevention of re-proliferation after surgery for established PVR.

Visual outcome

The causes of visual loss in PVR (and in uncomplicated retinal detachment) remain uncertain. Experimental studies have defined many of the events which follow neural retinal separation[42] and provide valuable pointers to potential pathology causing visual loss in human retinal detachment.

Irreversible photoreceptor loss is known to occur experimentally through apoptosis[43] and may be critical to visual recovery in human detachment and PVR. Photoreceptor damage may also be important and malapposition to underlying RPE can potentially cause misalignment of photoreceptors and visual acuity loss through the Stiles–Crawford effect, whereby light hitting the receptors obliquely is less effective at causing stimulation than that hitting axially. Plasticity of second order neurons has also been demonstrated in experimental retinal detachment[44] and the potential functional effects of such 'rewiring' in the retina are unknown.

Subretinal pathology, for example RPE multi-layering, has been shown to inhibit photoreceptor recovery or re-attachment.[42] Given the well documented proliferation of RPE cells in PVR, this change (and potentially also subretinal gliosis) could have profound effects on visual recovery. Retinal pucker and distortion caused by the contraction of epiretinal membranes is another potential factor leading to visual loss.

The effects of multiple vitreoretinal surgical interventions and potentially also the toxicity of agents used (silicone oil, for example, may be toxic to various intraocular tissues) are further possible causes of visual loss in PVR. A combination of the various factors outlined above may play a role in the poor visual outcomes seen in eyes with PVR (Table 1).

Retinal and peri-retinal pathology

We have recently analysed human retinectomy specimens obtained at vitrectomy surgery for established PVR with the aim of investigating the causes of visual loss and the potential for functional recovery. A combination of conventional light microscopy on semi-thin (1.5 μm) resin-embedded sections and immunohistochemistry using laser-scanning confocal microscopy were used together with primary antibodies to neural and non-neural retinal proteins, to macrophages and to RPE cells in a double-staining technique (see Lewis *et al*[44] for details).

As demonstrated by semi-thin histology, the overall retinal architecture was often relatively well preserved and the structural elements necessary for functional recovery appeared to be present (Figure 1). It was notable that the retina remained preserved despite detachment durations of between 8–12 weeks. Overlying epiretinal membranes generally had a complex, layered architecture with both cellular and extracellular matrix components. Focal glial 'bridges' (or 'pegs') were found extending from the inner retina to the membranes.

Epicentres of contraction ('star-folds') were identified where membranes were particularly thick and more often comprised predominantly of extracellular matrix (Figure 2). The retina in these eyes generally retained good architectural structure.

Immunohistochemical analysis using the confocal microscope demonstrated characteristic changes in both glial and neural elements of the retina. Photoreceptors

Table 1 Potential causes of visual loss in eyes with PVR

Photoreceptor loss/damage
Neural retinal damage/remodelling
Subretinal pathology—RPE/glial scars limiting photoreceptor recovery
Epiretinal membranes
Effects of treatment/toxicity
Optic neuropathy

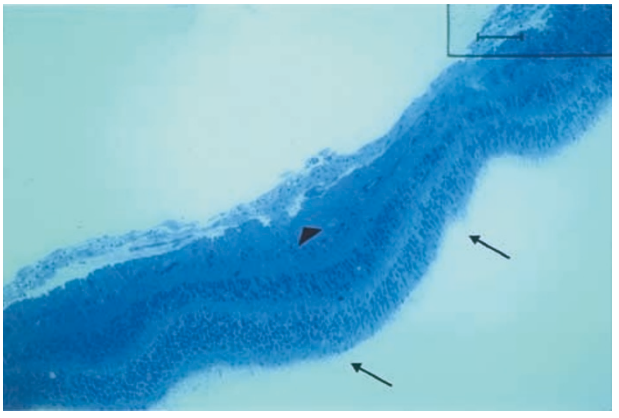

Figure 1 Toluidine blue-stained semi-thin (1.5 μm) section of human peripheral retinectomy. The retinal architecture is well preserved although photoreceptor inner and outer segments are absent (arrows). There is an overlying complex epiretinal membrane which has a continuous glial 'bridge' to the inner retina (arrowhead). Inner limiting membrane wrinkling is seen related to this. Scale bar = 100 μm.

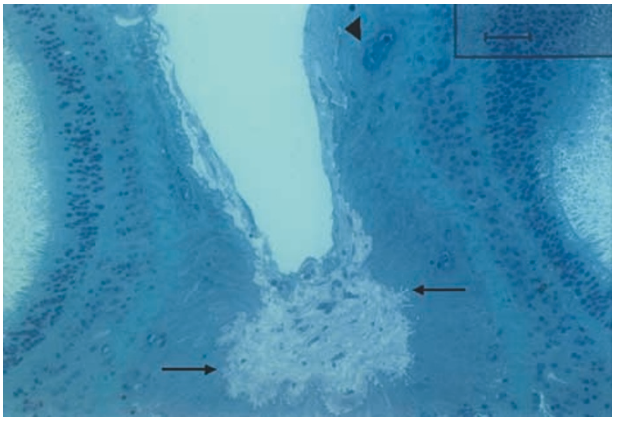

Figure 2 Toluidine blue-stained semi-thin (1.5 μm) section of human retinectomy showing a 'starfold'. The central membrane is thick and relatively acellular and has the appearance of contraction with marked wrinkling of the underlying inner limiting membrane (ILM) (arrows). Discontinuity of the ILM is also seen (arrowhead). Scale bar = 50 μm.

had a marked loss of outer segments with variable destruction of inner segments and redistribution of rod and cone opsins to the inner segment and cell body (Figure 3). Both rods and cones were however present in most of the sections examined. There was a marked extension of rod neuritis towards the inner retina—these processes often followed Muller cell trunks and were characteristically 'beaded' (Figure 3). These beads were often found to be positive for synaptophysin stain (data not shown). Second order neurones were also found to undergo a similar process of remodelling extending neurites into the outer retina (data not shown).

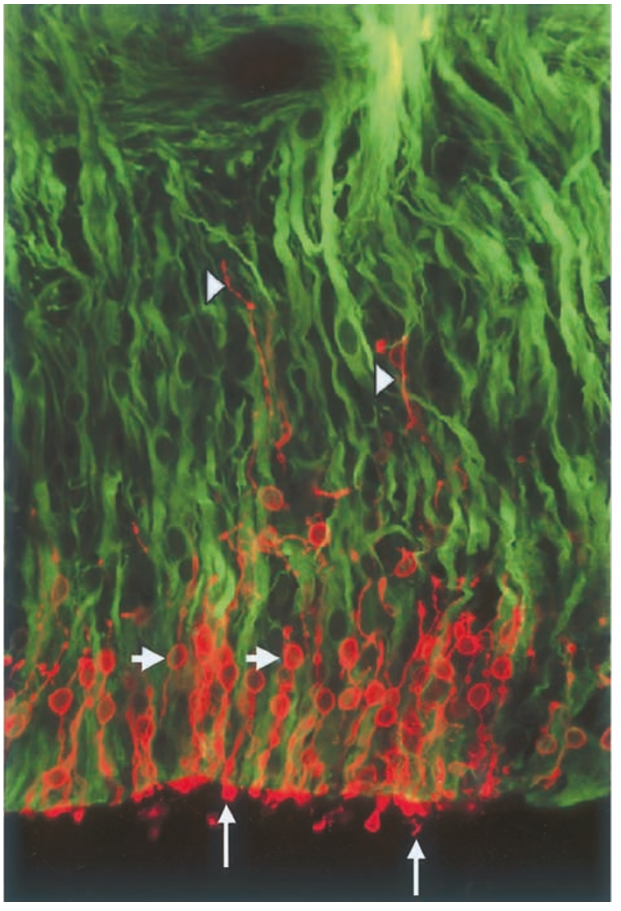

Figure 3 Confocal microscope immunohistochemistry of PVR retinectomy. GFAP = green, rodopsin = red. There is loss of photoreceptor inner and outer segments (arrows), redistribution of rodopsin to rod cell bodies (short arrows to examples) which have produced neurite extensions towards the inner retina (arrowhead). These processes often follow a Muller cell trunk and have a beaded appearance. There is a marked up-regulation of GFAP (green) staining in Muller cells.

Both glial fibrillary acid protein (GFAP) and vimentin staining of retinal glial cells were markedly up-regulated in retinectomies (Figures 3 and 4). Glial cell processes were found to penetrate the ILM and extend to the epiretinal space where they formed a component of epiretinal membranes (Figure 4). Similarly glial cell extensions were seen in the subretinal space, again in some cases forming confluent gliotic scars.

Conclusions

It is clear from the studies of retinal pathology in PVR that both neural and non-neural elements of the retina undergo an active process of remodelling. The functional consequences of these changes are uncertain, for example, glial cells could produce growth factors

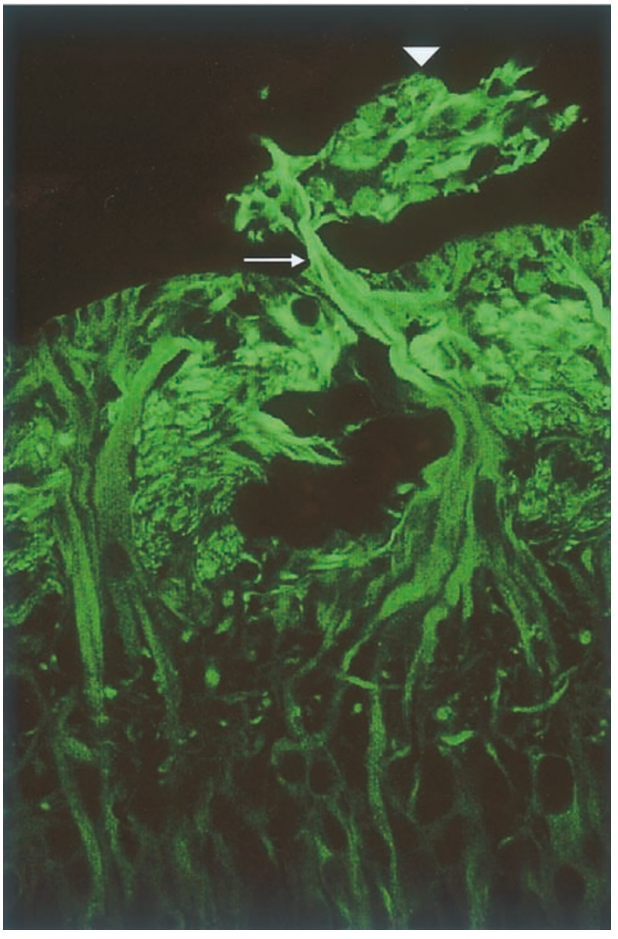

Figure 4 GFAP staining of PVR retinectomy. There is a general increase in glial staining and glial cell extensions that penetrate the ILM (arrow) to form a glial epiretinal membrane (arrowheads).

which can exacerbate the proliferative process but also potentially 'protect' the neural retina. The structural components necessary for functional recovery appear to be present, even in advanced detachment, although secondary pathology such as confluent subretinal gliosis may limit photoreceptor regeneration.

Aspects of the pathology also have a bearing on the surgical management of PVR. The glial continuity between retina and epiretinal membranes in the form of bridges or pegs may make surgical separation of anterior membranes and retina difficult or impossible. In this situation 'tearing' the membrane off may result in further trauma and produce glial cell activation: anterior retinectomy may be a better option. Cells in the very thick collagenous membranes seen for example in star-folds in established PVR may not be accessible by single exposure intravitreal anti-proliferative adjunctive medication. Direct surgical removal of membranes in established PVR may therefore be the only viable treatment at present, although sustained delivery systems have promise for the future. Research to prevent the development or recurrence of PVR and improve its visual outcome may eventually produce more widespread benefit in the management of primary retinal detachment and other forms of retinal disease.

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