

A Brief Review and Re-thinking of Proliferative Vitreoretinopathy

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Abstract

Prevention of proliferative vitreoretinopathy (PVR) continues to be a challenge for retinologists despite almost 30 years of research history. New diagnostic tools, based on the genetic profiles of patients with retinal detachment (RD), are now available. In addition, clinical trials in humans are about to begin of new pharmacological approaches, based on so-called 'biological agents'. Thus, it might be that, in the near future, it will be possible to reduce the incidence of PVR, which currently accounts for 8–10 % of all cases of RD.

Keywords

Genetic profile, intraretinal gliosis, proliferative vitreoretinopathy, reattachment rate, retinal detachment, visual acuity

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Proliferative vitreoretinopathy (PVR) is a major complication of rhegmatogenous retinal detachments (RD), with a prevalence of almost 10 %. It also accounts for approximately 75 % of all primary surgical failures. It was identified as an independent clinical entity in 1983 by the American Retina Society Terminology Committee, which proposed a classification of PVR into several stages (A–D3), which was widely accepted by both clinicians and researchers. This classification was amended in 1989 by the Silicone Study Group and has since undergone additional modifications.

Medical Treatments for Proliferative Vitreoretinopathy

When determining the classifications of PVR, much emphasis was put on the appearance of fibrous membranes over the surface of retina and vitreous that further contract, causing a tractional RD with poor prognosis, both anatomical and functional. The original classification also recognised the existence of subretinal membranes in some patients.

At the time of the original classification, retinal pigment epithelial cells (RPE) were identified as having a main role in the development of PVR. Therefore, intravitreal proliferation of fibroblast-like cells was considered a target for the prevention of this severe complication.

As a result, some antiproliferative agents were tested in animal models and in humans, although with disappointing results. These included the so-called 'British cocktail', a combination of low-molecular-weight heparin (LMWH) and 5-FU, first published in 2001 and which has not yet achieved widespread clinical use despite good preliminary results.

In this line of pharmacological manipulation, many attempts have been made to try to prevent the formation of extracellular matrix, further contractions of the membranes and the attachment of cells

to the new-formed scaffolds and more. However, all attempts failed when trialled against PVR in humans.

In the meantime, some clinical studies have tried to identify more accurately the clinical risk factors involved in the appearance of PVR, as well as to develop formulas to calculate the probability of patients with RD going on to develop this complication. Information regarding the clinical events associated with PVR is now available, but the formulas have neither been sensitive enough nor produced useful enough specificity values to be used in daily clinical work.

Unfortunately, research on PVR is not currently in fashion and retinologists are paying less attention to this complication. This is despite its prevalence remaining unchanged (between 8 and 10 %) and its anatomical and functional results being a 'catastrophe' for the patient.

Given that the prevalence of RD is almost 1.5 new cases per 10,000 inhabitants per year, PVR might affect up to 7,000 patients every year in a country such as Spain (with a population of 44 million people). Once PVR has appeared, the chances of having multiple surgeries increases for the patient, resulting in escalating costs for the healthcare system, as reported for the National Health Service in the UK in 2004.

Collaborative Studies of Proliferative Vitreoretinopathy

With the aim of providing additional information, two collaborative studies by several centres in Europe (Spain, Portugal, UK and Holland) have been underway since 2004, co-ordinated by the Eye Institute (IOBA) of the University of Valladolid (Spain). These studies, named Retina 1 and Retina 4, have already produced papers and more information is now being processed. These studies

are contributing greatly to the clarification of previous ideas and concepts relating to PVR.

Revision of Current Proliferative Vitreoretinopathy Classification

These collaborative studies have already shown that existing PVR classifications must be significantly revised. Although several proposals were made during the 1990s, the initial classification is still the most used in publications. However, few clinicians use it in clinical practice because it does not provide useful information, regarding neither the severity of the disease nor the activity of the scarring process. In addition, it does not take into account the existence of intraretinal changes that occur in many patients, adding severity to the situation and forcing surgeons to perform complicated procedures, such as large retinectomies.

Thus, a simpler classification has been proposed based on the existence of three types of PVR: epiretinal (the known membranes over the retina surface), subretinal (rare and frequently associated to previous surgical attempts or post-traumatic RD) and intraretinal (the most severe form). These three types of PVR can co-exist in some patients.

Intraretinal changes are caused mainly by reactive gliosis of the retina glial cells (Müller and astrocytes) and cause a shortening of the retina, creating a challenge for the surgeon who can have difficulty reattaching the retina. Thus, the identification of this type of intraretinal PVR is crucial for planning surgery and it is important information for the prognosis for each patient.

A similar situation to the use of different classifications of PVR in publications versus the clinical setting is also seen in other aspects of management of this disease, such as the experimental models developed to mimic it. For example, it is already known that cell proliferation is not a crucial part of PVR, although it is an important step. However, many new treatments were proposed based on experimental work using models receiving intravitreal injections of external cells, which are not at all typical of the pathogenesis of PVR. Evidence shows that such treatments failed and none are in routine clinical use.

Clinical Risk Factors

Currently, there are also clearer ideas of the importance of associated clinical risk factors. Although such factors are important, they do not determine the development of PVR. Therefore, as part of the Retina 1 and 4 studies, genetic factors implicated in this anomalous scarring

process have been explored. Single nucleotide polymorphisms (SNPs) have already been identified that, when present in a patient, clearly mark a high risk of that patient developing PVR. One of the most important SNPs, linked to lymphotoxin alpha (LTA), strongly related to the gene encoding tumour necrosis factor (TNF)- α , as published in 2010. In addition, there are other SNPs related to apoptosis that are awaiting publication.

In addition, although there is no doubt that RPE cells have an important role in the pathogenesis of PVR, other 'actors' are also being identified. Among these, activated macrophages initiating from the retinal tissue or from an external source are now considered to be important elements in PVR pathogenesis.

Proliferative Vitreoretinopathy Treatment Targets

Based on the current results from the two collaborative studies, new targets have been identified for preventing this complication. As mentioned above, for almost 30 years, attempts to treat PVR have been based on antiproliferative agents, with unsatisfactory results. Now, new approaches are being testing, such as the use of anti-TNF drugs and others. It is likely that prophylaxis could be achieved by a balanced combination of several agents and careful selection of the surgical technique, following the determination of the risk of that patient developing PVR based on their genetic profile.

A question that remains is the poor functional outcome of those patients whose retina was successfully reattached. Although this phenomenon also occurs in non-complicated RD, it is more important in those patients with associated PVR. According to data from Retina 1 and 4, published in 2008, <40 % of patients with RD and reattached retina achieved a visual acuity better than 20/40. This percentage fell dramatically in those patients with PVR.

Many factors are involved in this unsatisfactory functional result, some of which are well identified. During the past few years, interest in neuroprotection has gained in popularity, probably because the possibility of manipulating the survival of photoreceptors now seems an affordable prospect.

Concluding remarks

If RD cannot be avoided, challenges for the near future should be the prophylaxis of its most serious complication, PVR and the restoration of an adequate visual acuity to the patient. However, despite being identified almost 30 years ago, PVR remains a significant clinical problem. ■