

Treating peripapillary choroidal neovascular membranes: a review of the evidence

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REVIEW

Abstract

Peripapillary choroidal neovascular membranes (PCNM) are defined as a collection of new choroidal blood vessels, any portion of which lies within one disc diameter of the nerve head. There are two types of PCNM, and correct pre-interventional identification of growth site has been shown to stratify the chance of visual improvement following therapy. Clinical manifestations occur only where the membrane extends over the macula, if the vessels haemorrhage into the subretinal space or fluid exudation occurs within the macula. This review provides an update and overview on the diverse range of current treatment studies and strategies being used in present clinical ophthalmic practice.

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Introduction

Peripapillary choroidal neovascular membranes (PCNM) were first described in 1928 by Lopez and Green.¹ PCNMs account for 10% of all choroidal neovascular membranes with a female predilection.² A large period of time can elapse between the anatomical onset of the disease and visual deterioration. Clinical manifestations only occur if the membrane extends over the macula, if the vessels haemorrhage into the subretinal space, or fluid exudation occurs within the macula.³ PCNM can be described either by extent (comparing

its size in relation to the optic disc) or circumferentially (how many clock hours of the optic disc circumference is involved). Larger PCNMs have the added complication of causing visual loss by inducing scar contraction, haemorrhage, and further aggressive fibrovascular growth.⁴ A PCNM is considered large if it is more than 3.5 disc areas or involves more than 50% of the disc circumference.⁵ Regardless of size and aetiology, the natural course of untreated PCNM is extremely variable; ranging from spontaneous involution to fulminant enlargement towards the fovea. In the most simplistic form, one can consider the formation of PCNM akin to the Knudsen hit theory seen in the pathogenesis of colorectal cancer.⁶ In PCNM, the pathology affects the integrity of the peripapillary RPE–Bruch's membrane–photoreceptor complex. The first hit is an acquired or genetic damage to this axis that instigates an endogenous wound-healing response. Choroidal vessels either traverse through breaks within Bruch's membrane or extend around the termination of the membrane adjacent to the disc. Continual insults ('hits') lead to further remodelling, exudation, haemorrhage, and extension, thus finally compromising vision.¹ It is useful to categorise the various disease processes that have been shown to be associated with PCNM (Table 1).

In a large proportion of cases (up to 39%), the cause cannot be fully identified; as a result they are described as idiopathic.¹

There are two types of PCNM, and correct pre-interventional identification of the growth site of the membrane has been shown to stratify chance of visual improvement following therapy.⁷

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Table 1 Disease processes that can cause PCNM, divided into five distinct categories

<i>Degenerative</i>	<i>Inflammatory</i>	<i>Optic nerve malformations</i>	<i>Neoplastic</i>	<i>Vascular</i>	<i>Other</i>
ARMD	Birdshot retinochoroidopathy	Multiple evanescent white-dot syndrome (this is inflammatory)	Choroidal naevi	Polypoidal choroidal vasculopathy	Idiopathic
Angiod streaks	Chronic uveitis (only one case described in 1980)	Morning glory disc syndrome (one documented case)	Choroidal osteoma		
Degenerative myopia	Peripapillary choroiditis (3 cases documented)	Optic nerve drusen	Malignant melanoma (1 case noted)		
LASER photocoagulation scars (rare; usually in the setting of angiod streaks)	Peripheral uveitis (only one case documented in 1985)	Optic nerve pits			
Traumatic choroidal ruptures	Presumed ocular histoplasmosis syndrome (POHS) Sarcoidosis Serpiginous choroiditis	Pseudotumour cerebri Retinochoroidal colobomas Tilted disc syndrome (3 documented cases only)			

Type one

Commonly seen in patients with ARMD, in which the choroidal neovascular membrane is deep or within the retinal pigment epithelium. This is the most common cause of choroidal neovascularisation (CNV) in patients over 50.

Type two

The membrane is anterior to the pigment epithelium, usually seen in those with POHS.

Search criteria

A medline search was performed for all literature with the headline terms ‘peri-papillary choroidal neovascular membrane(s)’. The term ‘treatment’ was added to enhance specificity relevant to our investigation. No date restrictions were used.

Natural history

Reported figures suggest that PCNMs have very poor outcomes if left simply untreated, with up to 25% of patients deteriorating to 20/500 or worse after 3 years.⁴ It has been shown that better outcomes are seen in treating membranes early, whilst they are small and don’t affect visual acuity (VA).² The aim is to treat before the membrane encroaching the fovea, but the largest obstacle is these types of membranes generally are asymptomatic up until that stage.

Treatment modalities

Modern treatment options that have been explored include; laser, photodynamic therapy with verteporfin, surgery, and anti-VEGF agents. Unfortunately, any method of treating PCNM incurs the risk of damaging the papillo-macular bundle or the retinal pigment epithelium, with subsequent visual field defects. Thus, which modality of management is most beneficial to each unique case?

Laser

Laser was the first modality to be tried and as further experience was gained it became evident that PCNMs are notoriously difficult to treat because of the slow and unpredictable growth pattern leading to undefined margins. Guidelines from the Macular Photocoagulation Study (MPS) emerged to minimise the risk of thermal damage to the optic disc and retinal nerve fibre layer.⁸ Patients were deemed ineligible for laser treatment if:

- (1) The lesion was larger than 4.5 clock hours.
- (2) A large adjacent submacular haemorrhage was present.
- (3) 1.5 clock hours of temporal peripapillary retina was not spared.

The notion that laser treatment for such lesions is definitive and absolute has been refuted. There are reports that laser may actually have negligible to nil impact treating PCNM. A retrospective analysis over a 10-year period from the Western Eye Hospital, London,

compared the final visual outcomes after Argon laser treatment in relation to position and size of the membrane.² A total of 12 patients were treated with an average of two sessions per patient. Eighty percent of the PCNM arose temporal to the disc, closest to the fovea. The results showed no statistical significance on visual outcome with respect to position or size of membrane.² Moreover, there was no association between laser and visual outcome. Interestingly, this paper did show that small membranes, situated outside the macular vascular arcades have a good prognosis, regardless of whether treatment or conservative regime is adopted.

Furthermore, the pioneering MPS study championing the use of laser in PCNM can be interpreted as being misleading to the ophthalmic community. MPS included CNV associated with POHS in addition to ARMD.⁸ The results were flawed in the sense both macular and PCNM were included; these are distinct pathological entities and as such should be analysed separately. If one solely analyses the patients with PCNM in the study, the results were fairly uniform with respect to achieving final VA of 20/40 or better with laser photocoagulation (50% of patients) and no treatment (43%).⁸

Documented recurrence rates of neovascularisation post laser ablation therapy are up to 50%.⁹ It is important to note that half of these recurrences occurred from a site outside the treatment area; this highlights the importance of thorough investigation to highlight the full extent of pathology before treatment regime commencing. Recently, Wolf *et al*¹⁰ have shown that indocyanine green (ICG) choroidal angiography is superior to FFA in providing anatomic information of CNV. To circumvent this problem, the operator should have a wide margin of treatment at the edge of the membrane.

In summary, it is questionable whether laser is beneficial at all. Moreover, laser therapy also has the limitation of inducing thermal injury, scar formation, vitreous haemorrhage, branch arteriolar obstruction, and damage to the papillomacular bundle.¹¹ Hence, other modalities were pursued and researched.

Photodynamic therapy

Photodynamic therapy with verteporfin causes less local damage to tissues than laser according to the 'Treatment of age related macular degeneration with PDT' (TAP) study.¹² Although the full indications for PDT therapy are yet to be clarified, potential membranes should not extend closer than 200 μm to the edge of the optic nerve.¹³ The guideline recommendation for PDT with verteporfin infusion particularly advocates subfoveal located lesions.

Rosenblatt *et al*¹⁴ treated seven patients with PDT, who were not eligible for MPS entry. The authors included patients who had an active extrafoveal lesion, greater

than 4.5 clock surface of the temporal peripapillary area. The PCNM was secondary to ARMD in five patients and POHS in two; mean age was 58 years. All patients had a full resolution of activity of the membranes; five eyes required one treatment and two eyes were treated twice. VA improved from mean of 20/75 to 20/40 at the last follow-up.¹⁴ The authors suggested that PDT could be effective in extrafoveal lesions. Furthermore, a reduced dose of PDT may be effective as the authors postulated extrafoveal PCNM are less aggressive than subfoveal membranes.

The landmark TAP study advised that safety could be compromised if some or all of the optic nerve is included in the treatment field. Other schools of thought contradict this advice, suggesting that the studies revealing optic nerve damage were not in human subjects and furthermore used higher doses of PDT than that encountered clinically.¹⁵ Bernstein *et al* looked at the safety profile of PDT treatment with respect to optic nerve involvement by retrospectively reviewing seven patients consecutively treated for PCNM secondary to ARMD.¹⁶ Each patient was given at least one standard dose of verteporfin PDT (6 mg/m², 83 s laser exposure, 50 J/cm²), and the treatment zone included at least part of the optic nerve. Age ranges were 66–88 years and initial best-corrected VA (BCVA) varied from 20/50 to CF; the duration of follow-up varied from 3 to 33 months.¹⁶ No post-procedural complications were noted in any subject.

To summarise, PDT is effective at angiographic resolution of membranes but VA is less responsive. Concerns around collateral tissue damage exist, especially regarding optic nerve damage.

Surgery

Surgical measures were introduced in 1991.¹⁶ Surgical management involves vitrectomy and small retinotomy made adjacent to the membrane. The membrane is mobilised with a pick and is extracted with tamponading pressure. Younger patients have more favourable outcomes due to presumed greater ability to regenerate from the iatrogenic damage to the retinal epithelium.¹⁶ Only one paediatric patient with PCNM has been documented in the literature.¹⁷ In this paper, a 17 year old had surgical extraction of a POHS-related membrane. BCVA improved from pre-operative 20/200 to final post operatively of 20/60 at 29 months follow-up (4 Snellen line improvement).

A famous early trial highlighting the merits of intervention was the Submacular Surgery Trials Research Group. Patients with subfoveal CNV were randomised to observation (113) or surgical (112) groups.¹⁸ At 24 months, the median BCVA were 6/75 and 6/48,

respectively; however, this was not statistically significant. The greatest benefit was achieved with those eyes with a baseline VA of worse than 20/100.

Almony *et al*¹⁹ retrospectively analysed 40 (17 extrafoveal and 23 subfoveal) consecutive eyes presenting to the Barnes Retina Institute between 1992 and 2003. The median age was 35 years and all were ineligible for laser treatment as per the MPS guidelines because of extensive peripapillary involvement and extension within the fovea. The median BCVA improved from 20/200 to 20/50 post operatively in the subfoveal group; this represented a median improvement of 4 lines on the Snellen chart (comparing favourably with that achieved in the Submacular Surgical Trial²⁰). Approximately, 48% had VA better than 20/40, with only three cases experiencing a loss of vision greater than 6 lines.¹⁹ In the extrafoveal group, median BCVA improved from 20/60 to 20/20. This group had median improvement of 1 line on the Snellen chart. Approximately, 82.4% of cases had final BCVA of 20/40 or better and only one patient experienced greater than 6 lines of visual loss.¹⁹ These results are superior to those from the MPS trial. Overall, only eight patients out of 40 had a decline of vision after surgical management; six of these cases can be attributed to recurrent membrane formation (which was a poor prognostic indicator with respect to final VA). Blinder *et al*¹³ looked at patients with PCNM secondary to ARMD; this was a retrospective review describing the results of surgical management in patients who did not fit the MPS criteria or refused laser treatment. Patients were excluded if they had non-ARMD aetiology or the PCNM extended subfoveally; hence, 11 patients were included with a mean age of 78 years and mean size of 5 clock hours. Approximately, 64% of patients had improved or stable VA postoperatively; mean VA change was 1 line of visual improvement.¹³ Although not statistically significant, the authors noted an association whereby the most benefit in terms of improved VA was achieved in more elderly and those with worse eyesight at baseline.¹³ A limitation with the study was that the author excluded those patients whose membranes extended deep into the retinal epithelium; hence this was not a fair representation of the PCNM seen most commonly in ARMD. Aisenbrey *et al*⁴ performed an interventional consecutive case series evaluating the effect of surgical management, using both morphological and clinical end outcomes, in patients with PCNM secondary to ARMD. Eight patients over 50 years were included in this prospective study, with patients having subretinal fluid exudates, haemorrhage, and retinal pigment detachment. None of the PCNM extended into the fovea and median size was 4.5 clock hours (thus, ineligible for laser treatment⁴). Mean preoperative BCVA of 20/63 improved to 20/40

postoperatively, representing a statistically significant improvement of 2.0 lines at final follow-up.⁴ Four patients required cataract surgery at 6–13 months post-surgical intervention. One patient developed a peripheral retinal detachment after 5 years, although this did not affect the VA. Only one patient in the series did not have an improved VA because of the development of a branch retinal vein occlusion after 3 months. Results of the trial revealed that surgical management can be limited by complications, which include endophthalmitis, retinal detachment, and retinal haemorrhage. (Table 2)

In summary, outcomes from surgical treatment are promising, although study numbers remain low. Potential adverse effects related to intraocular surgery, including retinal detachment and endophthalmitis are rare but clinically significant when compared with non-penetrating treatment modalities. A larger study randomising comparable patient groups between best non-surgical practice and surgery is warranted.

Anti-VEGF treatment

One of the most exciting advances in the world of ophthalmology is the pharmacological manipulation of neovascularisation within the eye, thus preventing leaky vessel formation and traction. The landmark 'Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration' (²¹) and 'Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration' (²²) used subjects with classic, sub-foveal lesions. Nguyen *et al*²³ first described the clinical use of bevacizumab in PCNM. An early study by Pederson²⁴ assessed the impact of intravitreal bevacizumab (1 mg) in patients with subretinal CNV. The patients were assessed retrospectively, in an uncontrolled case series. A total of 26 eyes were followed up monthly for 6 months and received repeated injections as indicated clinically (set protocol with facility for extra injections at clinician discretion). Choroidal neovascular membranes of varying aetiologies were assessed in the study, but only one patient had PCNM. Unfortunately no functional improvement with respect to BCVA was noted after the 6-month period, but baseline Snellen acuity was maintained. However, structural improvement was seen on OCT.²⁴ In keeping with the rest of the literature, the authors did not specify the individual result of the patient with PCNM. Owing to the transient nature of improvement, the authors suggested that ideally each patient should have a unique regime with respect to how frequent the injections are administered.

Mansour *et al*¹⁸ performed a retrospective, consecutive case series of patients with inflammatory ocular

Table 2 Summary table of studies

Authors	Country	Year (published)	Journal	Number of eyes	Summary
Kies <i>et al</i> ⁹	UK	1988	Am J Ophthalmol	55	After laser treatment, PCNM recurred in some patients outside the treated complex.
Cialdini <i>et al</i> ¹¹	USA	1989	Ophthalmic Surg Lasers Imaging	27	Argon laser treatment led to improved or stabilised VA in 80% of patients. Argon green is superior to red.
Ruben <i>et al</i> ²	UK	1994	ACTA Ophthalmol. Scand.	20	There was no difference in final VA in relation to laser treatment, size of membrane, or position of membrane at presentation.
Capone <i>et al</i> ³	USA	1994	Arch Ophthalmol	30	Black patients have a spectrum of neovascular macuopathy distinct from the Caucasian population.
Gass <i>et al</i> ⁷	USA	1994	Am J Ophthalmol	5	Described the importance of recognising the type of CNV before considering surgical intervention.
Uemura <i>et al</i> ¹⁷	Japan	2000	Arch Ophthalmol	17	Paediatric patients have a good recovery of vision with surgical intervention (alternative to laser).
Blinder <i>et al</i> ¹³	Canada	2005	Ophthalmic Surg Lasers Imaging	11	Patients ineligible for laser treatment had surgery. Approximately 64% of patients had stable or improved VA.
Rosenblatt <i>et al</i> ¹⁴	USA	2005	Retina	7	In six eyes, at least 2 lines of improvement on the Snellen chart were achieved. A lower dose of PDT than standard was used.
Nguyen <i>et al</i> ²³	USA	2006	Br J Ophthalmol	2	Two case reports highlighting the value of avastin in PCNM secondary to high myopia.
Pederson <i>et al</i> ²⁴	Denmark	2007	ACTA Ophthalmol. Scand.	26	At 3 months post Avastin treatment, 22 patients had mean improvement of VA 2 letters on Snellen chart. The importance of tailored regimes of injection frequency were emphasised.
Aisenbrey <i>et al</i> ⁴	Germany	2007	Br J Ophthalmol	8	Post-surgical intervention; mean logMAR scores improved from 0.5 to 0.3.
Bernstein <i>et al</i> ¹⁶	USA	2008	Retina	7	All patients had improved VA and resolution of peripapillary haemorrhage following PDT treatment.
Mansour <i>et al</i> ¹⁸	Multi-centre	2008	Am J Ophthalmol	84	This can be used to treat lesions proximal to the disc. Patients with inflammatory ocular PCNM (variety of diseases) showed some short-term improvement with avastin.
Almony <i>et al</i> ¹⁹	USA	2008	Ophthalmology	40	Patients with POHS, ineligible for laser treatment, underwent surgery; 33 of the eyes achieved had stabilised or had better VA at final examination.
Figueroa <i>et al</i> ²⁵	Spain	2008	Br J Ophthalmol	6	At 13 months post Avastin treatment, VA improved in five eyes; mean improvement of four lines.
Hoeh <i>et al</i> ²⁶	Germany	2008	Eur J Ophthalmol	4	At 34 weeks after treatment with Avastin, two patients had markedly reduced VA and one had no change.

neovascularisation, secondary to a host of underlying aetiologies. Patients selected for intravitreal bevacizumab were those whom had failed conventional treatment, including systemic/periocular/intraocular steroids, laser, PDT, and surgery. This was a multi-centre trial, recruiting members from the American society of retinal specialists. The response to anti-VEGF treatment was classified by angiographic findings as complete, partial, or no response. Only 8 of the 42 cases were peripapillary; the average age was 39 years and all were Caucasians. The initial BCVA was mean 0.82 ± 0.36 (SD); post a mean 1.1 injections over a 3-month period led to an improvement to 0.47 ± 0.38 ($P = 0.01$).¹⁸ Moreover, central foveal thickness improved from 352 to 254 μm . In contrast to Pederson's study, Figueroa *et al*²⁵ looked

specifically at patients with PCNM to assess the affect of intravitreal bevacizumab on VA. This was a short multi-centred, interventional case series with six eyes from five patients in Madrid. Four were virgin eyes and two were treated after having previous surgery (5 months and 2 years previously, respectively). In five eyes, bevacizumab injection led to complete resolution of activity on both FFA and OCT. Moreover, there was a mean improvement of four lines in these five eyes. After mean follow-up of 13 months, no recurrences had developed.²⁵ This is the only series looking at anti-VEGF in the management solely of PCNM. These results are incredibly encouraging and should pave the way for an explosion of studies to arise on the scene. Caution must be reserved; a host of limitations existed with this trial

including short-term follow-up, unmasked researchers, variations in management between centres, and absence of standardised OCT examination.

Further caution should be exhibited as not all the literature has shown favourable results with respect to clinical outcome with anti-VEGF treatment. Hoeh *et al*²⁶ described their experiences with intravitreal bevacizumab in the treatment of four cases of PCNM. Follow-up was 34 ± 20 weeks, after an average of 3.5 ± 3.1 injections. In all patients, there was a morphological resolution of the membrane with no adverse side effects, but improvement in BCVA was variable amongst the population treated:

- Patient 1: 20/32 to 20/100 (eight injections over 63 weeks)
- Patient 2: 20/50 to 20/40 (two injections over 6 weeks)
- Patient 3: 20/80 to 20/200 (three injections over 13 weeks)
- Patient 4: 20/500 to 20/20 (one injection).

In summary, theoretically anti-VEGF treatment has the advantage over other management options in maintaining the integrity of the papillomacular bundle. However, general shortcomings of intravitreal anti-VEGF treatment exist currently as the duration of action is short, requiring multiple injections. There is a wealth of data showing the benefit of ranibizumab and bevacizumab in macular locations. Many studies exclude peripapillary membranes altogether and others fail to subanalyse membrane location with visual outcomes. There is a relative paucity in data directly analysing anti-VEGF effects on a pure population of peripapillary membranes. Therefore, at present there is no evidence base for treatment criteria or re-treatment strategy.

Conclusions

Having critiqued the existing literature, it is clear that limitations exist in our understanding. Each treatment modality has relative contraindications and varied success. Unfortunately because of the paucity of the disease seen in the general population, studies exhibit small number of subjects usually including patients in whom one treatment modality has already been tried and failed.

Although most peripapillary membranes are age-related in aetiology, we should continue to be aware of polypoidal choroidal vasculopathy (PCV) as a causative factor. Our understanding and detection of PCV as a pathogenic factor is growing. Membranes previously presumed secondary to ARMD may have a PCV aetiology in up to 25% of the subjects, especially in the Asian populations.²⁷ ICG angiography should therefore

be considered in all studies determining how subtypes of PCNM respond to treatment.

Most importantly, no studies exist directly comparing established treatments in a controlled and standardised setting. It seems logical that synergistic treatment with multiple treatment types may improve visual outcome. What we need most is a large prospective placebo-controlled study directly comparing the available interventions. Until this is performed, our management remains based on low-level clinical evidence.

Conflict of interest

The authors declare no conflict of interest.

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