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Major review

# Posner-Schlossman syndrome

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ABSTRACT

Posner-Schlossman syndrome, or glaucomatocyclitic crisis, is a unilateral ocular condition characterized by recurrent attacks of nongranulomatous anterior uveitis and raised intraocular pressure that can result in chronic secondary glaucoma. This relatively rare disease is most likely the result of recurrent cytomegalovirus infection and affects predominantly middle-aged males. Diagnosis is largely clinical, with aqueous and blood sampling aiding the identification of any underlying infectious cause. Successful disease management is often achieved by topical treatment, although systemic therapy and even surgical intervention may be required. We discuss our current understanding of Posner-Schlossman syndrome, from its pathophysiology through to recommended treatment options.



## 1. Introduction

Posner-Schlossman syndrome (PSS) was first described in 1948 as a condition characterized by recurrent, acute attacks of mild, unilateral, nongranulomatous, anterior uveitis accompanied by markedly elevated intraocular pressure.[51] During the acute attack, also referred to as glaucomatocyclitic crisis, anterior chamber drainage angles remain open, with visual fields and optic disks appearing normal. Vision may be mildly affected.[51] The acute and recurrent nature of the condition helped to differentiate PSS from other hypertensive uveitis entities such as Fuchs uveitis syndrome,[8] but initially not enough was known of the mechanistic drive underpinning the disease to allow for confident distinction between these similar conditions. PSS was originally deemed benign, but is now recognized as a relatively rare cause of chronic secondary glaucoma.[27,31,52] As such, optimum assessment, management, and follow-up of these patients are important. We provide a comprehensive description of the current understanding of PSS etiology, demographics, best management, and prognosis.

## 2. Disease etiology

Classically, it is accepted that infection, injury, and autoimmune drive can all contribute to uveitis. Thus, an external stimulus and an inherent response together determine the

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development and severity of disease. Important studies in recent years have helped to shine light on the pathogenesis of PSS but also suggest that they share common etiologies with other hypertensive uveitic conditions.

## 3. Infection

We now believe that the initial event that leads to PSS is an infection in the anterior chamber. Although a variety of organisms have been proposed by small isolated cases studies, the bulk of the literature supports the cytomegalovirus (CMV) as the leading cause.[7,8,20,30,37,38,40,53,63,67] Twenty years ago, the case was made for the herpes simplex virus (HSV) as a cause of PSS.[68] In a small study, the aqueous of 3 PSS patients tested positive for HSV genomic fragments, while testing negative for CMV and varicella zoster virus.[68] To our knowledge, however, no further evidence has emerged of a role for HSV in PSS. Serum antibodies against *Borrelia burgdorferi* have been shown to be raised significantly in patients with uveitis of varying forms compared to controls, but not in PSS patients.[24] In an isolated South Korean study, PSS patients had a significantly higher risk of testing positive for Anti-*Helicobacter pylori* immunoglobulin G in venous blood compared to controls (80% vs 56.2%).[13] The hypothesis for such a causal link is unproven. Furthermore, *H pylori* infection rates are higher in individuals from lower socioeconomic groups, so the fact that the control group was not controlled socioeconomically compromises the study. The observation is nevertheless interesting, but why a systemic stimulus would result in an eye disease that is always unilateral is uncertain.

Cytomegalovirus infection is ubiquitous worldwide, and the major site of involvement in the immunocompetent eye is the anterior chamber, where it is known to cause anterior uveitis[30] and endotheliitis.[35,36] The presence of CMV DNA in the anterior chamber by polymerase chain reaction (PCR) is a significant risk factor for a raised intraocular pressure in uveitic patients.[30] Proposed mechanisms are the development of 1) a thick and edematous trabecular band (trabeculitis), 2) trabecular blockage by pigments and chronic inflammatory cells, and 3) peripheral anterior synechiae with secondary angle-closure glaucoma. That said, little exists in the literature as to the gonioscopic appearance in PSS eyes. Furthermore, we do not know where the initial infection is located (iris, trabecular meshwork, corneal endothelium). Whatever the cause, increasing CMV DNA copy number raises the likelihood of pressure-lowering therapy being required.[30] This suggests CMV presence in the anterior chamber may be a cause of PSS,[63] and in a study of 48 consecutive PSS patients in Singapore who underwent aqueous biopsy, 18 (37.5%) tested positive for CMV DNA on PCR.[7] This study examined patients with a variety of uveitic conditions (Fuchs uveitis syndrome, endotheliitis) so it is of interest that 75% of positive biopsies (18 of 24) were in PSS patients. This figure was much less in another study (38%).[67] Thus, although CMV appears to be associated with the spectrum of acute uveitic conditions, patients are particularly at risk for PSS, suggesting involvement of the trabecular meshwork. A further study by the same authors found a slightly higher percentage of PSS patients to be CMV positive (52%),[8] whereas a small study in France found 5 of 7 PSS patients tested positive for CMV DNA in their aqueous.[67] In a small Iranian study, 4 of 10 (40%) PSS patients who underwent aqueous biopsy tested positive for CMV infection on PCR.[20] In east China, only 26.4% (14/53) of PSS patients' aqueous tested positive for CMV DNA[37] so its significance seems to vary globally.

PCR detection of CMV DNA has long been validated, with a high sensitivity (80.1%) and specificity (93%) from blood,[2] and this sensitivity is maintained by multiplex testing of aqueous samples.[12] Despite this variability (possibly reflecting differing rates of endemic infection), the correlation is obvious. In all these studies, the control group (matched patients undergoing routine cataract surgery) had very low levels of CMV DNA in their aqueous. This is supported by the finding that a high CMV copy number in the anterior chamber is also predictive of endotheliitis and Fuchs.

CMV genotype polymorphisms were investigated in a small group of patients, with glycoprotein B type 3 and UL144 type 1 variants shown to be common genotypes of CMV present in the anterior chamber.[45] This subset is distinct from the CMV variants which cause retinitis, which could be a reflection of differing modes of entry into the eye. CMV retinitis tends to occur along retinal arteries, indicating that it originates from the vasculature. Furthermore, CMV retinitis is most closely associated with HIV infection, or at the very least the immunocompromised, hinting at a different pathogenesis. It has been seen in immunocompetent patients,[48] but distinctions were drawn. CMV retinitis in non-HIV patients was associated with a vitritis and, in 64% of patients, anterior segment inflammation. Furthermore, these patients often had raised intraocular pressure (IOP) and endotheliitis. Why CMV-associated anterior segment disease is so prevalent yet CMV retinitis is almost exclusively a disease of the immunocompromised remains to be determined, but the aforementioned evidence suggests that immunosuppression allows CMV entry to the eye via the retinal vasculature. Interestingly, 71.4% of CMV-positive PSS patients in one study were male,[38] hinting that genetic variability may play a role in PSS development. To determine other contributing factors, allelic heterogenicity has been investigated in recent years.

## 4. Allellic heterogenicity

In a Chinese population of 100 PSS patients and matched controls, the allele frequency of HLA-C*1402 was significantly higher in PSS patients.[73] Other allelic and haplotype frequency differences, while initially appearing significant, did not stand up to Bonferroni correction, which accounts for the issue of multiple comparisons. Nevertheless, the suggestion that HLA-C polymorphisms are associated with PSS hints at a role for genetic variants of immune regulation in PSS pathogenesis.[73] Genetic variants are known to be reflected in altered inflammasome/cytokine profiling and so this has been investigated.

## 5. Aqueous cytokine profile

In a prospective study of 143 patients, uveitic glaucoma patients (including those with PSS) undergoing trabeculectomy

were found to have significantly higher levels of interleukin (IL)-6, IL-8, monocyte chemoattractant protein-1, tumor necrosis factor-α, and vascular endothelial growth factor in their aqueous compared to healthy controls undergoing cataract surgery.[44] Furthermore, the levels of IL-6, monocyte chemoattractant protein-1, and vascular endothelial growth factor were higher in uveitic glaucoma cases than in primary open-angle glaucoma cases also undergoing trabeculectomy. Uveitic patients with cells in their anterior chamber at the time of surgery were found to have higher levels of IL-8, tumor necrosis factor-α, and PDGF-AB/BB than those without activity.[44] What is not known is whether a higher anterior chamber cytokine level is a predisposing factor for development of glaucoma in a PSS patient.

An earlier study had also reported a raised IL-6 in PSS aqueous compared to control, along with IL-5, CXCL8, CCL2, CCL4, TGFB, and G-CSF[38]; however, they reported a lower expression of TNF-a, along with IL-2, IL-12, IFNa, and GM-CSF. No significant difference was seen between IL4, IL13, IL17, IL10, CXCL9, CXCL10, and IFNy. These studies' findings are not entirely concordant, but the ability to differentiate PSS aqueous from that of controls by cytokine profiling would serve to argue that, although PSS may be triggered by CMV infection, the clinical manifestations are affected by the immune-mediated inflammatory reaction, which varies according to the patient. In keeping with this hypothesis, PSS is a recurrent condition that responds to steroids. No significant difference in cytokine expression levels was seen between CMV-positive and CMV-negative PSS patients.[38]

## 6. Vascular endothelial dysfunction

It has previously been shown that vascular endothelial cell dysfunction is a risk factor for both normal-tension and primary open-angle glaucoma.[60] Attenuated retinal and optic nerve head autoregulation resulting from this dysfunction has been postulated to lead to an unstable oxygen supply, a relevant component in the pathogenesis of glaucoma.[19] A small prospective case-control study also showed that flow-mediated vasodilation (as measured by ultrasound following occlusion of the brachial artery) was perturbed in PSS patients.[55] This equates to endothelial cell dysfunction, with non–endothelium-dependent (nitroglycerin mediated) vasodilation showing no difference between case and control. It would be a reasonable proposal that endothelial dysfunction is a predisposing factor for development of glaucomatous optic neuropathy in PSS patients as a result of their pressure spikes; however, no mention is made in this study of glaucomatous changes in the patients. What is less certain is the mechanism whereby perturbed small-vessel autoregulation predisposes a patient to the acute attacks of irodocyclitis. This could be the result of attenuated uveoscleral outflow, but much more work is needed to support and clarify this finding. We find it nevertheless interesting as commonly used drugs such as hydroxymethylglutaryl coenzyme-A reductase inhibitors (statins) and calcium channel blockers reportedly improve flow-mediated vasodilation.[16] The same study found homocysteine and C-reactive protein levels were equivalent between the groups.[55]

With allelic variance and endothelial dysfunction possibly contributing to PSS severity, the demographics of the disease populations (Table 1) are important.

## 7. Demographics

### 7.1. *Age*

Although PSS has been reported in a 13 year old,[4] it is otherwise exclusively a disease of adults. In a European study, the highest incidence was reported in a 20–29 age bracket,[47] whereas in the Far East, onset appears later. The mean age of diagnosis varies between 32.6 and 58.92 years.[7,8,13,27,28,38,42,43,55,56,67]

### 7.2. *Sex*

Aside from a single study reporting the majority of PSS patients identified as being female (56.6%),[38] all other reports show men to be more at risk of disease with numbers varying from 50.5–71.4%.[8,13,27,28,47,55] In a small Iranian study, all cases (10) were male.[20]

### 7.3. *Intraocular pressure*

IOP at the time of presentation of PSS is uniformly high across all published data sets. Mean IOP in published studies varies from 42.77 mm Hg to 49.2 mm Hg.[8,13,20,27,55,56]

## 8. Geography

Most PSS studies have documented patient cohorts in the Far East, with rates of disease in Japan and Singapore ranging from 1.7% to 4.3% of all uveitis diagnoses.[28,42,43,56] Rates in northern Europe appear similar,[44] but the development of glaucoma is higher, with rates varying from 6.5% to 11.4% of all uveitic glaucoma.

### 8.1. *Diagnosis*

PSS diagnosis is a clinical one, with characteristic recurrent attacks of mild, unilateral, nongranulomatous, anterior uveitis accompanied by markedly elevated intraocular pressure.[51] Diffuse iris atrophy may be present. Anterior chamber drainage angles remain open, with visual fields and optic disks initially appearing normal. Vision may be mildly affected. If PSS fails to respond to steroids, it has been suggested a CMV infection of the anterior chamber is highly likely,[22] with 93% of steroid-recalcitrant patients having CMV detectable by PCR in their anterior chamber tap. This distinction is crucial in determining disease management (see the following).

CMV infection can, alternatively, cause a corneal endotheliitis.[69] Indeed, it is responsible for a quarter of endotheliitis cases in some populations.[29] CMV endotheliitis produces characteristic coin-shaped lesions, made up of medium-sized circumferential keratic precipitates with associated stromal edema.[5,22,35] These lesions are seen as an irregularly

**Table 1 – Summary of PSS case series**

| Study | Age at presentation (years) | Sex | Presenting IOP | Geography | % CMV +ve |
|---|---|---|---|---|---|
| Paivonsalo-Hietanen et al, Acta Ophth Scand 2007 | Range, 20–29 | 5M:2F | — | Finland | — |
| Chee et al, AJO 2008 (883-9) | Mean, 39.2 | 40M:27F | 49.2 ± 10.8 mm Hg | Singapore | 52.2% |
| Chee et al, BJO 2010 | Range, 26–69 | 30M:20F | — | Singapore | All in study |
| Chee et al, AJO 2008 (834-40) | Range, 18–74 | 16M:7F | 43.5 ± 9.8 mm Hg | Singapore | All in study |
| Choi et al, Eye 2010 | Mean, 43.8 ± 13.0 | 26M:14F | 40.3 ± 12.3 mmHg | South Korea | — |
| Jap et al, Ophth 2001 | Mean, 35; range, 17–61 | 28M:22F | 48.16 mm Hg | Singapore | — |
| Kanda et al, BJO 2014 | Range, 14–90 (NB uveitic glaucoma; only 6.5% of cohort have PSS) | 47M:46F | — | Japan | — |
| Li et al, PLoS One 2012 | Mean, 54.6; range, 24–72 | 23M:30F | — | China | 26.4% |
| Nakahara et al, Ocul Immun Inflamm 2014 | — | 14M:6F | — | Japan | — |
| Shen et al, IOVS 2010 | Mean, 36.6; range, 18–50 | 7M:5F | 45.8 ± 3.1 mm Hg | Taiwan | — |
| Shimizu et al, Clin Ophth 2014 | Mean, 58.92 ± 12.51 | 8M:4F | 42.77 ± 7.9 mm Hg | Japan | — |
| Woo et al, Ocul Immunol Inflamm 2015 | Range, 27–77 | 10M:6F | 35.68 mm Hg | Singapore | All in study |
| Heydayatfar et al, Int Ophth 2014 | Mean, 44.5; range 32–63 | 10M:0F | 36–48 mmHg (range) | Iran | 40% |

CMV, cytomegalovirus.

thickened, highly reflective endothelial cell layer on anterior segment OCT.[71] Confocal microscopy demonstrates the presence of large endothelial cells containing nuclei with a high reflection area surrounded by a halo of low reflection, resembling an owl's eye, within the cornea.[57] These "owl eye cells," deemed to be CMV-infected corneal endothelial cells with an intranuclear inclusion body and seen in other tissues of CMV-infected patients, show an association with the coin-shaped lesions.[72] This clinical picture described has a high positive predictive value (90.9%) of anterior chamber CMV infection.[22] CMV endotheliitis can also be associated with an immune ring formation (akin to that seen in HSV-related keratitis)[10] or a nodular endothelial lesion surrounded by a translucent halo with or without associated brown pigment,[8] as demonstrated by anterior segment OCT.[66] It can be responsible for precipitating corneal graft rejection[59] (detectable by PCR both in the aqueous and the rejected graft stroma) but if CMV is detected early enough, correct treatment (see the following) can successfully save the transplant.[29]

Ophthalmologists must recognize these signs as CMV PSS and endotheliitis demonstrate marked overlap,[67] with endotheliitis being strongly associated with a raised IOP in some studies,[6,34] resulting in endotheliitis patients requiring medical and/or surgical pressure management.

### 8.2. *Differential diagnosis*

PSS must be differentiated from other causes of raised intraocular pressure. Differentiation from acute angle closure glaucoma can be made by gonioscopic examination and the absence of features characteristic of angle closure glaucoma (fixed, dilated pupil and, to a lesser extent, severe pain, nausea, and vomiting). The acute and recurrent nature of the attacks, together with its positive response to steroids, helps to differentiate it from Fuchs uveitis syndrome.[51]

The uveitic glaucomas have features similar to PSS. Glaucoma was seen in 19.7% of a uveitic population (1099 patients).[62] Although PSS showed the highest incidence of glaucoma, sarcoid, HSV, Behcet's, HLAB27 uveitis, Vogt-Koyanagi-Harada disease, and human T-lymphotropic virus type 1 uveitis all predisposed patient to the disease. These conditions should therefore always be considered when dealing with uveitis with elevated IOP. A high IOP not in keeping with the mild iridocyclitis and absence of posterior or peripheral anterior synechiae should help to differentiate PSS from these other forms of uveitis; however, serological and aqueous testing is warranted if clinical distinction cannot be made.

Undiagnosed anterior uveitic patients responding poorly to conventional topical steroid therapy have a high likelihood of viral infection. Of those who underwent aqueous sampling, 66% tested positive for CMV, HSV, VSV, or rubella.[37] Of note, those with elevated IOPs were more likely to test positive for CMV (75%).[34] HSV and varicella zoster virus infection can also lead to raised IOP, so other clinical signs may help in differentiating from CMV infection. Studies have reported some clinical manifestations (Table 2) more common with CMV-associated PSS than non-CMV PSS. Compared to other HSV and HZV, CMV-associated PSS is more common in male. Presence of corneal endotheliitis with coin-shaped lesion and linear keratitic precipitates are more common in CMV infection. Sectoral iris atrophy is more common with HSV and HZV infection than CMV infection.[67] In spite of the aforementioned differences, there are no specific signs, and the clinical manifestations overlap between CMV and non–CMV-associated PSS. A definitive diagnosis can only be done by qualitative PCR analysis.

HSV is a prevalent viral pathogen globally that, after initial infection, establishes a latent state in the trigeminal ganglion during which viral DNA is maintained within neuronal nuclei before reactivation.[54] Episodes of reactivation produce classic epithelial dendrites and/or stromal keratitis (stromal opacities and edema) that eventually leads to scarring, neovascularization, and corneal hypoanesthesia.[26] Varicella zoster virus initially presents as *Herpes zoster ophthalmicus* with erythematous skin lesions (macules, papules, vesicles, and

**Table 2 – Clinical manifestations of CMV-associated PSS[34,67]**

| PSS (CMV) | PSS (non-CMV) |
|---|---|
| Corneal endotheliitis with coin-shaped lesion | No coin-shaped lesion |
| Linear KPs similar to rejection line | Any patterns of KPs |
| More common in male | No preponderance |
| Diffuse iris atrophy more common than sectoral | No specific pattern |

CMV, cytomegalovirus; PSS, Posner-Schlossman syndrome; KPs, keratitic precipitates.
Although the aforementioned clinical findings can help in the clinical diagnosis of CMV-associated Posner Schlossman syndrome, the clinical manifestations can be overlapping between non–CMV-associated PSS.

pustules that eventually crust) in the distribution of the trigeminal nerve. Hutchinson's sign, defined as skin lesions at the tip, side, or root of the nose, is a strong predictor of ocular inflammation in herpes zoster ophthalmicus. Sectoral iris atrophy is suggestive of HSV or varicella zoster virus infection. When assessing a patient, it must always be kept in mind that different infections can occur sequentially, with a previous case reporting CMV-positive PSS in 1 eye followed by HSV-positive keratouveitis in the other.[70] Correct diagnosis, particularly the distinction between those that are CMV positive and negative, is important in planning the management of PSS patients.

## 9. Management

### 9.1. *Medical*

Patients with PSS should have their inflammation controlled with topical steroids and their raised IOP addressed with topical antiglaucoma therapies as a first line. Evidence is now emerging that eliminating CMV from the anterior chamber with valganciclovir leads to improved disease control.

A retrospective study of 15 patients demonstrated topical ganciclovir (with or without oral ganciclovir) led to a significant reduction in uveitis flare ups posttreatment.[1] The study was too small to compare oral versus topical therapy. IOP control was an issue as patients had had at least 24 months of disease before ganciclovir treatment, which would have resulted in significant trabecular meshwork damage.[1] In a larger study, 100% of CMV-positive PSS eyes had complete resolution of disease after 1 month of topical ganciclovir (2%), allowing cessation of steroid and glaucoma drops (mean drop reduction 1.78–0.88).[61] Despite continued topical ganciclovir, recurrence was seen in 36.76% of CMV-positive eyes with chronic meshwork inflammation (PAS, pigmented meshwork) meaning 32% of these eyes required filtration surgery. Surgery was significantly higher in CMV-positive eyes beyond 5 years. The rate of PSS flare-ups in CMV-positive eyes reduces from 84.61% to 57.14% if topical ganciclovir is continued long term.[9] It should be noted that successful disease attenuation using topical ganciclovir in the aforementioned studies was achieved using 2% gel. Although 1 case report found it to be effective,[49] previous attempts using 0.15% ganciclovir in a cohort of patients had resulted in subtherapeutic aqueous concentrations and poor remission rates.[7] A recent study reported role of topical ganciclovir (0.15%) in reducing the frequency of recurrence in patients with CMV-related uveitis. Ganciclovir was started 6 times a day and then tapered to 3–4 times a day as a maintenance dose for long term.[64] It appears from the aforementioned studies that 2% topical ganciclovir is associated with less chance of recurrence, less endothelial cell loss, and better control of intraocular pressure.[61]

Hwang and colleagues in a prospective case series of 6 patients reported the efficacy of intravitreal ganciclovir with or without oral antiviral.[21] The initial dose of ganciclovir injected was 2 mg in 0.05 mL and then followed by maintenance dose with oral valganciclovir. The follow-up period was short at 14.7 months.

The benefits of oral valganciclovir have been assessed retrospectively.[65] Thirteen CMV-positive patients had their inflammation-related IOP significantly reduced and were on significantly less IOP-lowering therapies (mean follow-up 17.2 months). Recurrence of disease, however, was seen (38.5% of patients) following cessation of the antiviral. A large retrospective study comparing topical, oral, and intravitreal applications of valganciclovir for CMV hypertensive uveitis showed that, although topical therapy had a higher failure rate compared to oral treatment (36% vs 9%), the recurrence rate was lower (57% vs 80%) over a 27.7-month follow-up.[9] Recurrence for those receiving any form of valganciclovir was high after cessation of treatment (75%). This is most likely because it is virostatic rather than virucidal, but ocular immune privilege may contribute to preventing total eradication of the infection.[9] Thus, a long-term maintenance course of topical valganciclovir following the successful disease treatment using systemic valganciclovir may be effective at preventing relapses. In a prospective study of 11 uncontrolled CMV-positive PSS patients, oral valganciclovir led to reduction of inflammation and IOP (mean 45 mm Hg to 16 mm Hg) within 1 week.[58] Long-term valganciclovir (mean 14 months) led to continued disease control in 63.4% of patients.

Intravitreal valganciclovir was advocated following a prospective study of 6 patients with uncontrolled CMV hypertensive uveitis.[22] Inflammation and IOP were controlled (mean follow-up 14.7 months) although no mention was made about cessation of steroids/IOP modulators. We question the necessity of intravitreal administration for what is essentially anterior chamber disease. Both oral and intravitreal valganciclovir reduce aqueous CMV to undetectable levels.[7] It must be noted that oral valganciclovir risks leukopenia,[1] and *in vitro* studies have hinted at a potential for corneal endothelial cell cytotoxicity if the drug is administered locally.[14]

Following the diagnosis of PSS, we recommend topical steroid and IOP-lowering medication as a first-line treatment. To our knowledge, no evidence exists that determines the best first-line IOP-lowering therapy. We advocate a carbonic anhydrase inhibitor, which is effective even if patients have a severe trabeculitis. Baseline visual fields, disk photographs, and OCT of the optic disc should be obtained. There should be a low threshold for an AC tap if the patient is not improving, with commencement of empirical topical valganciclovir.

Three-months of oral valganciclovir[9] should be considered if no improvement is seen, with careful monitoring of the patient's white-cell count. Careful tapering of treatment should be implemented after disease control with access to quick referral routes into secondary ophthalmology care established should symptoms return. Relapses should be treated with long-term oral valganciclovir. If IOP cannot be controlled medically, surgical intervention should be considered.[17]

### 9.2. *Surgical*

Filtration surgery is an option in the management of PSS. There are arguments for and against this practice. Although a filtering bleb may help drain inflammatory cells from the anterior chamber, thus reducing the severity of uveitic attacks, the uveitic conjunctiva contains more fibroblasts, lymphocytes, and macrophages than in control eyes, thus increasing the risk of surgical failure from scarring.[3]

In a retrospective cohort of 50 PSS patients, 17% required mitomycin C trabeculectomy. The surgery had an 80% success rate in controlling IOP spikes during disease flare ups,[27] and operated eyes appeared to have less PSS events overall. This apparent protection supports the theory of inflammatory cells migrating through a bleb, thus reducing AC activity and trabeculitis.

In a retrospective Japanese study of 101 uveitic glaucoma eyes undergoing mitomycin C–augmented trabeculectomy, the success rate was slightly lower: 71.3% in uveitic glaucoma, compared to 89.7% for primary open-angle glaucoma (mean follow-up 34.7 months).[25] Previous cataract surgical had a negative impact on success. Surgical complications were not higher in uveitic eyes.

Trabectome surgery has also been proposed to control IOP in PSS.[46] Seven uncontrolled CMV-positive PSS patients had their mean IOP reduced from 40 mm Hg to 13 mm Hg and mean IOP medications reduced from 3.1 to 0.8 (12-month follow-up). No patient had a disease recurrence throughout follow-up. Deep sclerectomy has been proposed as an effective treatment for raised IOP in PSS.[5] One study comparing deep sclerectomy to trabeculectomy found that, although IOP outcomes were comparable, deep sclerectomy procedures required more postoperative adjustments.[18]

In a retrospective review, 50% of PSS patients required surgery for uncontrolled raised pressure.[55] Of 47 uveitic glaucoma patients undergoing pressure-lowering surgery, success rates were 82.86% for trabeculectomy, 62.50% for trabeculotomy, and 75.00% for trabectome.[55] Postoperative uveitis was a negative predictor for surgical success.

One isolated case report documented the use of an Ahmed valve to lower IOP in a patient with PSS and recalcitrant raised pressure[63]; however, the authors did not comment on the success of the surgery. To our knowledge, there is no other evidence in the literature of tube surgery results in PSS patients and no published evidence as to the use of corneal grafting specifically for endothelial loss in PSS. Both PK (penetrating keratoplasty) and Descemet stripping and endothelial keratoplasty, however, have been effectively used in chronic uveitis.[50] Failure rates of Descemet stripping and endothelial keratoplasty (50%) for uveitis-induced endothelial dysfunction are higher than for other causes of endothelial cell dysfunction (13%).[50]

We thus advocate antimetabolite-augmented trabeculectomy as the surgical procedure to perform on PSS patients whose IOPs are uncontrolled by conventional medical therapy. Preoperatively, all attempts should be made to control inflammation, and careful postoperative follow-up should ensue. Subsequent cataract surgery should be treated in the same way.

## 10. Prognosis

PSS flare-ups may develop with relatively mild symptoms. As a result, the eye can suffer high pressures for some time before patients seek treatment. Early studies showed concomitant glaucomatous optic neuropathy at presentation to be as high as 45%.[31,51] Therefore, patients at risk of glaucoma, for example those with a large cup-to-disk ratio, should be treated prophylactically. Furthermore, case reports have highlighted the relative danger to the optic nerve, with nonarteritic anterior ischemic optic neuropathy[23] and optic atrophy[32] both demonstrated in eyes with attacks of PSS. Thus, we believe patients with known PSS and risk factors for ischemic optic neuropathy, including those with very small cup-to-disk ratios, should be prophylactically treated with pressure-lowering medication.

A more comprehensive, recent study found that glaucoma developed in 26.4% of PSS patients.[27] Although no evidence exists as to whether prolonged bouts of inflammation lead to glaucomatous field loss, the total duration of disease is, unsurprisingly, a predictor of glaucoma progression: 2.8 times higher with disease duration over 10 years compared to less than 10 years.[27] Age of onset and number of attacks were not predictive of glaucoma progression, despite transient hemodynamic changes that occur at the optic nerve head during acute attacks.[15] Seventeen percent of patients needed filtration surgery,[27] and this appears higher in CMV-positive patients (13.24% vs 1.72%).[61] This is most likely due to CMV causing more disease recurrences and longer bouts of inflammation, with the overwhelming majority of CMV-positive patients presenting with a raised IOP (91.7%),[30] Although the correlation between CMV and progression to glaucoma has been questioned,[8] a higher CMV copy number increases the number of pressure-lowering drops required.[30] CMV also results in significantly lower endothelial cell counts (1498/$mm^2$ vs 2040/$mm^2$).[29,61] Indeed, the higher the CMV viral load in the aqueous, the greater the endothelial cell loss.[41] This group did not correlate higher viral load to higher IOP, but all patients involved in the study had been referred by ophthalmologists and had therefore already had glaucoma therapy commenced. When patients present with CMV endotheliitis, pretreatment corneal edema and coexisting glaucomatous optic neuropathy are predictors of visual loss. Unsurprisingly, longer duration of PSS predicts visual field loss.[11] In one study, iris atrophy developed in 38.8% of PSS patients, and 14.8% had cataracts.[8] Isolated series/case reports have shown IOP to be stable in PSS eyes during general

anesthesia,[33] and S Cone ERG b-waves to be reduced during flare-ups.[39]

## 11. Conclusion

PSS is a relapsing form of iridocyclitis and a relatively rare cause of secondary glaucoma. Its stereotypical clinical picture makes it relatively easy to diagnose, but PSS has marked overlap with other forms of anterior segment inflammation, particularly that of corneal endotheliitis. The overwhelming evidence suggests that the pathogenesis of PSS is infection of the anterior chamber, most commonly by cytomegalovirus, and clinicians should have a high index of suspicion and a low threshold for performing aqueous biopsy to detect the virus by PCR. Why glaucomatocyclitis develops in some patients and endotheliitis in others remains to be resolved and will be a focus of research in the future. A definitive model has yet to demonstrate trabeculitis as the definitive cause of PSS pressure spikes. This is a key piece of evidence that a well-designed animal study could determine. Further work is also required to determine why certain patients are predisposed to such a marked pressure spike following infection by what is, in certain parts of the world, an endemic virus.

## 12. Literature search statement

For this review, a systematic search of the literature on Posner Schlossman Syndrome was performed. This included a search of MEDLINE using the following keywords: Posner, Schlossman, Posner- Schlossman, Posner-Schlossman Syndrome, and Glaucomatocyclitic Crisis. Non–English-language articles were included when translation was possible. All levels of publications including case reports and small case series were included, without any exclusion criteria due to the relative infrequency of reports and studies on Posner Schlossman Syndrome.

## 13. Disclosures

None of the authors have any financial/conflicting interests to disclose. The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article. R.M. is part-funded by an Academy of Medical Sciences Starter Grant (Wellcome Trust) and an Institutional Strategic Support Fund (ISSF) grant (Wellcome Trust).

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