Sympathetic Ophthalmia

37

Anna Marmalidou and Chukwuemeka Nwanze

Introduction

In 1813 the 3-year-old son of a harness maker stabbed himself in the right eye while playing with one of his father's awls resulting in loss of vision in the traumatized eye. Shortly thereafter, the boy's left eye became inflamed, and 2 years later he had lost vision in the non-traumatized eye leaving him completely blind. Approximately 10 years later, this boy, Louis Braille, invented the most commonly used tactile writing system for the blind [1]. This alphabet was named braille after the inventor.

The clinical scenario depicted above is the typical presentation of patients afflicted with sympathetic ophthalmia (SO). SO is a rare, bilateral, and diffuse granulomatous intraocular inflammation that occurs in most cases within days or months after either surgery or penetrating trauma to one eye. The clinical features of SO have been known since antiquity. The earliest known description of SO in literature is a paper by Agathias in an anthology compiled from Constantius Cephalis dating from 1000 AD [2]. SO was initially named sympathetic ophthalmitis in 1840 by Sir William Mackenzie, a Scottish ophthalmologist, who presented a series of six cases in which a penetrating injury to one eye led to bilateral blindness [3].

Epidemiology

Most of the literature about the incidence of SO dates from the 1960s to 1980s [4–8]. These studies suggest an incidence with a range of 0.2–0.5 % following penetrating ocular injuries and 0.01 % after intraocular surgery. There are two more recent studies from the United Kingdom (2000) [9] and China (2009) [10]. The UK study estimated the minimum rate of SO to be 0.03 per 100,000. The Chinese study estimated that SO occurred at a rate of 0.37 % after open globe injury. The results of both of these studies are within the range of previously published articles. There are approximately 3.1 penetrating eye injuries per 100,000 person/year in the United States [11]. This implies approximately 9,800 penetrating eye injuries in the United States during 2013 [12]. These estimates suggest that during 2013 there were approximately 98 new cases of SO in the US.

A. Marmalidou (✉)
Department of Ophthalmology, Massachusetts Eye and Ear Infirmary, Harvard Medical School, 243 Charles Street, Boston, MA 02114, USA
e-mail: anna_marmalidou@meei.harvard.edu

C. Nwanze
Department of Ophthalmology, Boston Medical Center, 85 East Concord St., Boston, MA 02118, USA

G.N. Papaliodis (ed.), *Uveitis*,
DOI 10.1007/978-3-319-09126-6_37

Males are at increased risk for eye trauma compared to females [13–15], thus SO resulting from ocular trauma tends to affect males more commonly [2, 5, 8, 16]. Similarly, given the higher rates of ocular trauma in younger patients, the age distribution of trauma-related SO cases is skewed lower [8, 17]. However, contemporary trends such as increased child safety monitoring and prophylactic medical/surgical measures may be reversing these trends in SO [16]. Surgery-induced SO does not show any gender predilection. Since older patients undergo more ocular surgery, surgical-induced SO tends to affect older patients [9, 17].

Clinical Presentation

SO has been reported to occur as early as 10 days [18] or as late as 66 years [19] after the penetrating trauma/surgical procedure. The peak incidence of SO occurs between 1 and 2 months after the inciting injury [20]. Most cases of SO (70–80 %) occur between 2 weeks and 3 months of the causative event [21]. 90 % of SO occurs within 1 year of the injury [20].

Patients who have SO typically present with ocular injection, pain, photophobia, epiphora, and insidious loss of vision in the non-injured eye [8, 22, 23]. These patients may also present with diminished near vision, a result of changes in accommodative amplitude [23, 24]. These symptoms are often accompanied by worsened inflammation in the injured eye [25]. Non-ocular symptoms are rare and include hearing disturbances, high-frequency deafness, vitiligo, poliosis, alopecia, and meningismus [23, 26, 27]. Clinical symptoms and signs are variable and can range from mild to severe [25, 28].

The slit lamp exam of patients with SO can reveal conjunctival injection and ciliary flush (limbal injection) [8, 22, 23]. The cornea may have granulomatous (mutton fat) precipitates or small white keratic precipitates [23, 28]. The anterior chamber has cell and flare in approximately 67 % of cases [8]. The iris may be thickened from lymphocytic infiltration and posterior synechiae may form. Intraocular pressure may be elevated as a result of synechiae and clogging of the trabecular meshwork with inflammatory debris. Alternatively, the eye pressure may be low secondary to ciliary body shutdown from the inflammation [22].

The posterior segment exam reveals moderate-to-severe vitritis (see Fig. 37.2). Papillitis, choroiditis, macular edema, migration of pigment into inner retinal layers, retinal vasculitis, and serous retinal detachments may also occur [21, 24]. Yellow-white choroidal lesions occur in the posterior pole and mid-equatorial region. These lesions may become confluent over time. These lesions correspond pathologically to Dalen-Fuchs nodules (see Fig. 37.1) [22, 25]. Dalen-Fuchs nodules appear in approximately one-third of eyes enucleated for SO [21, 29]. The Dalen-Fuchs nodules are not pathognomonic of sympathetic ophthalmia as they may be seen in other granulomatous inflammatory diseases such as Vogt–Koyanagi–Harada syndrome and sarcoidosis [25, 30]. Dalen-Fuchs nodules may represent the more severe spectrum of SO [25, 31].

Findings in chronic SO include cataract, glaucoma, choroidal neovascularization, subretinal fibrosis, atrophy of the optic nerve/retina/choroid, and finally phthisis bulbi [22, 24].

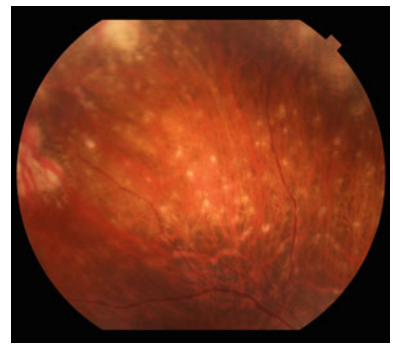

Fig. 37.1 Peripheral Dalen-Fuchs nodules in a patient with sympathetic ophthalmia

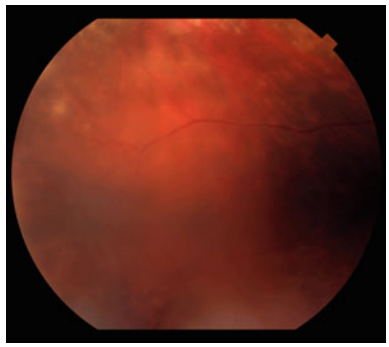

Fig. 37.2 Retinal vasculitis, vitritis, and inferior serous retinal detachment in a patient with sympathetic ophthalmia

Testing

There are no blood studies to confirm the diagnosis of sympathetic ophthalmia. Clinical investigations in SO include fluorescein angiography (FA), indocyanine green angiography (ICG), B-scan ultrasonography (US), optical coherence tomography (OCT), and pathological sections of enucleated eyes.

FA in the early venous phase demonstrates multiple hyperfluorescent areas that then demonstrate late leakage at the level of the RPE [22, 29]. Leakage occurs in Dalen-Fuchs nodules and areas of retinal vasculitis [24]. Early blocking is seen in areas occupied by Dalen-Fuchs nodules. The optic nerve head often stains in SO even in cases without optic nerve head edema [24]. Late pooling can be seen in the posterior pole representing multiple, lobular, serous retinal detachments [32].

ICG shows multiple hypofluorescent spots without a hyperfluorescent collar in the intermediate phase. Some of these areas become isofluorescent in the late stage [33–35]. These hypofluorescent areas are thought to correspond to choroidal edema and choroidal inflammatory infiltration [24]. Large areas of hypofluorescence can be detected in the late phase of ICG [35].

US in SO is used to detect gross anatomic changes in the retina and choroid. US can demonstrate diffuse thickening of the choroid as well as serous retinal detachments [36–38].

OCT in SO can be used to detect micro-anatomic changes within the retina. Observable OCT findings in SO include serous retinal detachments, intra-retinal edema, disintegration of RPE, tears in the RPE, elongation of photoreceptors, and disorganization of the retinal layers [29, 38–40]. Dalen-Fuchs nodules on OCT appear as hyper-reflective lesions at the level of the RPE with disruption of the inner segment/outer segment (IS/OS) junction [38, 41].

Pathological sections of eyes with SO (both the injured and the secondarily involved eye) demonstrate marked swelling of the choroid that corresponds to lymphocytic infiltration of the choroid. The inflammatory response is characterized as a diffuse, non-necrotizing, granulomatous inflammation of the entire uvea [22, 29, 42, 43]. Major cell types include epithelioid cells and some giant cells [2]. However, the cellular response is variable from case to case which may explain the wide spectrum of clinical presentations [44]. In severe cases, eosinophils and plasma cells can be observed, especially around the inner choroid [45]. Severe cases are also associated with the presence of pigment in the epithelioid cells [46]. The inflammation, typically but not always, spares the choriocapillaris [21, 45, 47].

Dalen-Fuchs nodules appear in approximately one-third of SO cases [21, 22]. Dalen-Fuchs nodules on pathological sections appear as yellow-white lesions of the mid-periphery, located in the choroid, typically between the RPE and Bruch's membrane [22, 25]. The RPE overlying the nodules is usually intact, but can vary from atrophic to hypertrophic [42, 44]. Histologically, the Dalen-Fuchs nodules are composed of lymphocytes, histiocytes, and epithelioid cells covered by an intact dome of RPE [22, 42, 44].

Pathogenesis

SO has been reported after trauma to the eye including non-penetrating trauma with hyphema, perforated corneal ulcers, penetrating foreign bodies, perforating foreign bodies, and malignant melanoma [21, 48–50]. SO has similarly been

described as a sequelae from surgical procedures such as trans-scleral cyclo-destructive laser, cataract surgery, paracentesis incisions, iridectomy, irradiation of choroidal melanomas, evisceration, retinal surgeries such as pars plana vitrectomy, and scleral buckling. SO has also resulted from accidental surgical perforation of the eye and from post-surgical endophthalmitis [29, 51–60]. Regardless of the nature of the instigating injury, the ultimate initiating factor is the disruption of the immune privilege of the eye. The immune privilege of the eye is a result of blood–ocular barriers in the retinal vascular endothelium, epithelium of the RPE, retinal and ciliary blood vessels; the absence of lymphatics in the eye, except for the conjunctiva; and a host of tightly regulated molecular expression profiles and atypical immunologic cascades [25, 61–68]. Once these barriers are breached, intraocular proteins are exposed to the immune system and an immunologic reaction against these antigens is initiated. Animal studies have shown that an SO-like syndrome can be induced in mammals with the peripheral (non-ocular) injection of proteins such as rhodopsin, interphotoreceptor retinoid-binding protein, recoverin, and soluble retinal antigen (S antigen) [69–73].

The initial presentation of the intraocular antigens to immune cells is via major histocompatibility molecules (MHC) and the process is regulated via several cytokines. It is hypothesized that certain MHC molecules, as a result of differential inter-molecular interactions, present intraocular proteins more successfully to immune cells. Similarly, certain cytokine variants are more or less able to induce a successful immune reaction. Thus, individuals with certain MHC and/or cytokine types are more likely to develop SO. It follows that the severity of the manifestations of SO might also be affected by the specific types of cytokines or MHC molecules that the individual possesses. Several variants of cytokines and their associated proteins, for example tumor necrosis factor (TNF)-α, TNF-β, TNF receptor 2, and cytotoxic T-lymphocyte-associated protein (CTLA) 4 and interleukin 10 (IL-10), have been shown to be either promote or protect against SO. Patients with these cytokine variants differ both in the severity of their clinical presentation and the amount of steroids they required to control their disease [74, 75]. Similarly, patients with certain MHC variants, such as HLA-DR4, HLA-DRw54, HLA-Bw54, HLA-DRB1*04, and HLA-DQA1*03, are more susceptible to SO and develop more severe variants of SO [76, 77].

Treatment

There are essentially two broad approaches to the management of SO: preventative by removal of the inciting ocular tissues and/or therapeutic with immunosuppressive/anti-inflammatory treatment.

Enucleation of the injured eye as a treatment for SO was first advocated for by Pritchard in 1851 who suggested that enucleation be performed once the uninjured eye showed signs of serious inflammation [78]. This recommendation was controversial because in some cases enucleation did not impact the course of the disease [2]. A study by Reynard et al. [79] demonstrated that early enucleation, which was defined as enucleation within 2 weeks of the inciting injury, resulted in better visual acuity in the uninjured eye, irrespective of treatment with corticosteroids. A subsequent multivariate logistic regression analysis of these data reaffirmed the conclusion that enucleation prior to 2 weeks after the injury resulted in reduced rates of SO. However, it was noted that eyes with good visual potential should not be enucleated [80]. Generally, enucleation of injured eyes with poor visual potential within 2 weeks of injury reduces but does not eliminate the risk of SO. Evisceration of the eye has also been used as a method to prevent SO [81]. There is a healthy ongoing controversy about the relative benefits of evisceration (improved cosmesis, surgical ease, and surgical risk) vs. enucleation (reduced risk of SO) [82–88].

Immunosuppression is used to treat sympathetic ophthalmia after it becomes manifest. Prior to the use of corticosteroids, approximately 50–60 % of eyes affected by SO became permanently blind [7, 23, 47]. By the last 1970 (well after the introduction of corticosteroids), as many

as 64 % of patients who had been treated with corticosteroids had vision 20/60 or better. The cost of visual preservation in these patients was the steroid-associated side effects, with most patients developing Cushing's syndrome [7]. More modern corticosteroid treatment involves high-dose oral corticosteroids (e.g., 1.0–2.0 mg/kg/day prednisone) continued for a period of 3 months. This is administered with adjunctive topical steroids and cycloplegics as dictated by anterior chamber inflammation. Steroids are subsequently tapered off and the response to treatment is evaluated. Pulsed intravenous steroids (methylprednisolone 1 g/day for 3 days), followed by oral steroids, may be beneficial in severe cases [22, 89].

In an effort to reduce the systemic side effects of corticosteroids, the use of intravitreal steroids may enable reduction of the quantity of systemic steroids that may be required [22].

Some cases of SO are refractory to steroids or require high doses of steroids for prolonged duration that can cause systemic side effects. These cases have been managed with steroid sparing immunomodulatory therapy including cyclosporine, tacrolimus, chlorambucil, cyclophosphamide, methotrexate, mycophenolate mofetil, and azathioprine [22, 25, 90–95]. The preceding drugs can be toxic and can have severe long-term sequelae including infertility and secondary malignancies [28]. Moreover, these agents require the physician to have competence in prescribing these agents and managing complications that may ensue. Current therapy has shifted toward less toxic and more directed immunomodulatory molecules. There have been several reports of SO patients that have responded to treatment with anti-TNF-α monoclonal antibodies including adalimumab and infliximab [96–98].

In the future, with the advent of "personalized medicine," patients may be genotyped to risk stratify those who are more likely to develop severe variants of SO and treated more aggressively to prevent ocular damage.

Conclusion

Sympathetic ophthalmia is a relatively rare, bilateral granulomatous panuveitis that occurs more commonly after penetrating trauma but also described after intraocular surgical procedures. The initiating event compromises the immune privilege of the eye and induces intraocular inflammation. Systemic corticosteroids are the initial treatment implemented, but these patients often require steroid sparing immunomodulatory therapy to control the uveitis and avoid steroid-associated toxicity.

References

1. Bullock JD, Galst JM. The story of Louis Braille. Arch Ophthalmol. 2009;127:1532–3.
2. Albert DM, Diaz-Rohena R. A historical review of sympathetic ophthalmia and its epidemiology. Surv Ophthalmol. 1989;34:1–14.
3. MacKenzie W. A practical treatise on diseases of the eye. 3rd ed. London: Longmans; 1840.
4. Allen JC. Sympathetic ophthalmia, a disappearing disease. JAMA. 1969;209:1090.
5. Liddy L, Stuart J. Sympathetic ophthalmia in Canada. Can J Ophthalmol J Can Ophtalmol. 1972;7:157–9.
6. Gass JD. Sympathetic ophthalmia following vitrectomy. Am J Ophthalmol. 1982;93:552–8.
7. Makley TA Jr, Azar A. Sympathetic ophthalmia. A long-term follow-up. Arch Ophthalmol. 1978;96:257–62.
8. Marak GE Jr. Recent advances in sympathetic ophthalmia. Surv Ophthalmol. 1979;24:141–56.
9. Kilmartin DJ, Dick AD, Forrester JV. Prospective surveillance of sympathetic ophthalmia in the UK and Republic of Ireland. Br J Ophthalmol. 2000;84:259–63.
10. Zhang Y, Zhang MN, Jiang CH, Yao Y. Development of sympathetic ophthalmia following globe injury. Chin Med J. 2009;122:2961–6.
11. Smith D, Wrenn K, Stack LB. The epidemiology and diagnosis of penetrating eye injuries. Acad Emerg Med Official J Soc Acad Emerg Med. 2002;9:209–13.
12. Annual Estimates of the Resident Population for Selected Age Groups by Sex for the United States, States, Counties, and Puerto Rico Commonwealth and Municipios: April 1, 2010 to July 1, 2013 In: U.S. Census Bureau PD, editor. June 2014.

13. Wong TY, Klein BE, Klein R. The prevalence and 5-year incidence of ocular trauma. The Beaver Dam eye study. Ophthalmology. 2000;107:2196–202.
14. May DR, Kuhn FP, Morris RE, et al. The epidemiology of serious eye injuries from the United States Eye Injury Registry. Graefe's Arch Clin Exp Ophthalmol (Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie). 2000;238:153–7.
15. Wong TY, Lincoln A, Tielsch JM, Baker SP. The epidemiology of ocular injury in a major US automobile corporation. Eye (London, England) 1998;12(Pt 5):870–4.
16. Sen HN, Nussenblatt RB. Sympathetic ophthalmia: what have we learned? Am J Ophthalmol. 2009;148:632–3.
17. Chan CC, Mochizuki M. Sympathetic ophthalmia: an autoimmune ocular inflammatory disease. Springer Semin Immunopathol. 1999;21:125–34.
18. Stafford WR. Sympathetic ophthalmia. Report of a case occurring ten and one-half days after injury. Arch Ophthalmol. 1965;74:521–4.
19. Zaharia MA, Lamarche J, Laurin M. Sympathetic uveitis 66 years after injury. Can J Ophthalmol J Can Ophtalmol. 1984;19:240–3.
20. Goto H, Rao NA. Sympathetic ophthalmia and Vogt-Koyanagi-Harada syndrome. Int Ophthalmol Clin. 1990;30:279–85.
21. Lubin JR, Albert DM, Weinstein M. Sixty-five years of sympathetic ophthalmia. A clinicopathologic review of 105 cases (1913–1978). Ophthalmology. 1980;87:109–21.
22. Damico FM, Kiss S, Young LH. Sympathetic ophthalmia. Semin Ophthalmol. 2005;20:191–7.
23. Chaithanyaa N, Devireddy SK, Kishore Kumar RV, Gali RS, Aneja V. Sympathetic ophthalmia: a review of literature. Oral Surg Oral Med Oral Pathol Oral Radiol. 2012;113:172–6.
24. Chu DS, Foster CS. Sympathetic ophthalmia. Int Ophthalmol Clin. 2002;42:179–85.
25. Albert DM, Miller JW, Azar DT. Albert & Jakobiec's principles and practice of ophthalmology. Philadelphia: Saunders/Elsevier; 2008.
26. Nirankari MS, Khanna KK, Chawla GD, Mathur RP. Sympathetic ophthalmitis with total deafness (a case report). J All India Ophthalmol Soc. 1970;18:29–32.
27. Comer M, Taylor C, Chen S, Martin K, Jordan K, Meyer P. Sympathetic ophthalmia associated with high frequent deafness. Br J Ophthalmol. 2001;85:496.
28. Nussenblatt RB. Sympathetic Ophthalmia. In: Uveitis Fundamental and Clinical Practice. St. Louis: Mosby; 2004. pp. 311–23.
29. Chu XK, Chan CC. Sympathetic ophthalmia: to the twenty-first century and beyond. J Ophthalmic Inflammation Infect. 2013;3:49.
30. Moorthy RS, Inomata H, Rao NA. Vogt-Koyanagi-Harada syndrome. Surv Ophthalmol. 1995;39:265–92.
31. Jennings T, Tessler HH. Twenty cases of sympathetic ophthalmia. Br J Ophthalmol. 1989;73:140–5.
32. Burkholder BM, Dunn JP. Multiple serous retinal detachments seen on wide-field imaging in a patient with sympathetic ophthalmia. JAMA Ophthalmol. 2014;132:1220.
33. Bernasconi O, Auer C, Zografos L, Herbort CP. Indocyanine green angiographic findings in sympathetic ophthalmia. Graefe's Arch Clin Exp Ophthalmol (Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie). 1998;236:635–8.
34. Moshfeghi AA, Harrison SA, Ferrone PJ. Indocyanine green angiography findings in sympathetic ophthalmia. Ophthalmic Surg Lasers Imaging Official J Int Soc Imaging Eye. 2005;36:163–6.
35. Saatci AO, Pasa E, Soylev MF, Kocak N, Durak I, Kaynak S. Sympathetic ophthalmia and indocyanine green angiography. Arch Ophthalmol. 2004;122:1568–9.
36. Castiblanco C, Adelman RA. Imaging for sympathetic ophthalmia: impact on the diagnosis and management. Int Ophthalmol Clin. 2012;52:173–81.
37. Arevalo JF, Garcia RA, Al-Dhibi HA, Sanchez JG, Suarez-Tata L. Update on sympathetic ophthalmia. Middle East Afr J Ophthalmol. 2012;19:13–21.
38. Varghese M, Raghavendra R. Dalen Fuch's nodules and serous retinal detachment on optical coherence tomography in sympathetic ophthalmitis. Indian J Ophthalmol. 2013;61:245–6.
39. Mahendradas P, Avadhani K, Madhavarao B, et al. High definition spectral domain optical coherence tomography of retinal pigment epithelial rip in a case of sympathetic ophthalmia. J Ophthalmic Inflamm Infect. 2013;3:19.
40. Gupta V, Gupta A, Dogra MR, Singh I. Reversible retinal changes in the acute stage of sympathetic ophthalmia seen on spectral domain optical coherence tomography. Int Ophthalmol. 2011;31:105–10.
41. Muakkassa NW, Witkin AJ. Spectral-Domain optical coherence tomography of sympathetic ophthalmia with Dalen-Fuchs nodules. Ophthalmic Surg Lasers Imaging Retina. 2014:1–3.
42. Jakobiec FA, Marboe CC, Knowles DM 2nd, et al. Human sympathetic ophthalmia. An analysis of the inflammatory infiltrate by hybridoma-monoclonal antibodies, immunochemistry, and correlative electron microscopy. Ophthalmology. 1983;90:76–95.
43. Chan CC, Nussenblatt RB, Fujikawa LS, et al. Sympathetic ophthalmia. Immunopathological findings. Ophthalmology. 1986;93:690–5.
44. Reynard M, Riffenburgh RS, Minckler DS. Morphological variation of Dalen-Fuchs nodules in sympathetic ophthalmia. Br J Ophthalmol. 1985;69:197–201.
45. Croxatto JO, Rao NA, McLean IW, Marak GE. Atypical histopathologic features in sympathetic ophthalmia. A study of a hundred cases. Int Ophthalmol. 1982;4:129–35.
46. Marak GE Jr, Font RL, Zimmerman LE. Histologic variations related to race in sympathetic ophthalmia. Am J Ophthalmol. 1974;78:935–8.

47. Winter FC. Sympathetic uveitis; a clinical and pathologic study of the visual result. Am J Ophthalmol. 1955;39:340–7.
48. Dada T, Kumar A, Sharma N. Sympathetic ophthalmia associated with antecedent adherent leucoma–a rare association. Acta Ophthalmol Scand. 1998;76:380–1.
49. Easom HA. Sympathetic Ophthalmia Associated with Malignant Melanoma. Arch Ophthalmol. 1963;70:786–90.
50. Bakri SJ, Peters GB 3rd. Sympathetic ophthalmia after a hyphema due to nonpenetrating trauma. Ocular Immunol Inflamm. 2005;13:85–6.
51. Fankhauser F, Kwasniewska S, Van der Zypen E. Cyclodestructive procedures. I. Clinical and morphological aspects: a review. Ophthalmol J Int Ophthalmol Int J Ophthalmol Zeitschrift fur Augenheilkunde 2004;218:77–95.
52. Wang WJ. Clinical and histopathological report of sympathetic ophthalmia after retinal detachment surgery. Br J Ophthalmol. 1983;67:150–2.
53. Chan CC, Roberge RG, Whitcup SM, Nussenblatt RB. 32 cases of sympathetic ophthalmia. A retrospective study at the National Eye Institute, Bethesda, Md., from 1982 to 1992. Arch Ophthalmol. 1995;113:597–600.
54. Abu El-Asrar AM, Al Kuraya H, Al-Ghamdi A. Sympathetic ophthalmia after successful retinal reattachment surgery with vitrectomy. Eur J Ophthalmol. 2006;16:891–4.
55. Lyons C, Tuft S, Lightman S. Sympathetic ophthalmia from inadvertent ocular perforation during conventional retinal detachment surgery. Br J Ophthalmol. 1997;81:612.
56. Bechrakis NE, Muller-Stolzenburg NW, Helbig H, Foerster MH. Sympathetic ophthalmia following laser cyclocoagulation. Arch Ophthalmol. 1994;112:80–4.
57. Edward DP, Brown SV, Higginbotham E, Jennings T, Tessler HH, Tso MO. Sympathetic ophthalmia following neodymium:YAG cyclotherapy. Ophthalmic Surg. 1989;20:544–6.
58. Fries PD, Char DH, Crawford JB, Waterhouse W. Sympathetic ophthalmia complicating helium ion irradiation of a choroidal melanoma. Arch Ophthalmol. 1987;105:1561–4.
59. Brour J, Desjardins L, Lehoang P, et al. Sympathetic ophthalmia after proton beam irradiation for choroidal melanoma. Ocular Immunol Inflamm. 2012;20:273–6.
60. Rathinam SR, Rao NA. Sympathetic ophthalmia following postoperative bacterial endophthalmitis: a clinicopathologic study. Am J Ophthalmol. 2006;141:498–507.
61. Zhou R, Caspi RR. Ocular immune privilege. F1000 biology reports 2010;2.
62. Yamada J, Streilein JW. Induction of anterior chamber-associated immune deviation by corneal allografts placed in the anterior chamber. Invest Ophthalmol Vis Sci. 1997;38:2833–43.
63. Streilein JW. Molecular basis of ACAID. Ocular Immunol Inflamm. 1997;5:217–8.
64. Streilein JW. Regulation of ocular immune responses. Eye (London, England) 1997;11(Pt 2):171–5.
65. Streilein JW, Dana MR, Ksander BR. Immunity causing blindness: five different paths to herpes stromal keratitis. Immunol Today. 1997;18:443–9.
66. Streilein JW, Ksander BR, Taylor AW. Immune deviation in relation to ocular immune privilege. J Immunol. 1997;158:3557–60.
67. Streilein JW, Takeuchi M, Taylor AW. Immune privilege, T-cell tolerance, and tissue-restricted autoimmunity. Hum Immunol. 1997;52:138–43.
68. Taylor AW, Alard P, Yee DG, Streilein JW. Aqueous humor induces transforming growth factor-beta (TGF-beta)-producing regulatory T-cells. Curr Eye Res. 1997;16:900–8.
69. Schalken JJ, Winkens HJ, Van Vugt AH, De Grip WJ, Broekhuyse RM. Rhodopsin-induced experimental autoimmune uveoretinitis in monkeys. Br J Ophthalmol. 1989;73:168–72.
70. de Kozak Y, Sakai J, Thillaye B, Faure JP. S antigen-induced experimental autoimmune uveo-retinitis in rats. Curr Eye Res. 1981;1:327–37.
71. Gery I, Chanaud NP 3rd, Anglade E. Recoverin is highly uveitogenic in Lewis rats. Invest Ophthalmol Vis Sci. 1994;35:3342–5.
72. Gery I, Wiggert B, Redmond TM, et al. Uveoretinitis and pinealitis induced by immunization with interphotoreceptor retinoid-binding protein. Invest Ophthalmol Vis Sci. 1986;27:1296–300.
73. Hirose S, Kuwabara T, Nussenblatt RB, Wiggert B, Redmond TM, Gery I. Uveitis induced in primates by interphotoreceptor retinoid-binding protein. Arch Ophthalmol. 1986;104:1698–702.
74. Atan D, Turner SJ, Kilmartin DJ, et al. Cytokine gene polymorphism in sympathetic ophthalmia. Invest Ophthalmol Vis Sci. 2005;46:4245–50.
75. Glover N, Ah-Chan JJ, Frith P, Downes S, Atan D. Unremitting sympathetic ophthalmia associated with homozygous interleukin-10-1082A single nucleotide polymorphism. Br J Ophthalmol. 2008;92:155–6.
76. Kilmartin DJ, Wilson D, Liversidge J, et al. Immunogenetics and clinical phenotype of sympathetic ophthalmia in British and Irish patients. Br J Ophthalmol. 2001;85:281–6.
77. Davis JL, Mittal KK, Freidlin V, et al. HLA associations and ancestry in Vogt-Koyanagi-Harada disease and sympathetic ophthalmia. Ophthalmology. 1990;97:1137–42.
78. Pritchard A. Srugical cases admitted under Augustine Pritchard, Esq, Surgeon to the Infirmary. Bristol R Infirmary Provincial Med Surg J. 1851;18:66–7.
79. Reynard M, Riffenburgh RS, Maes EF. Effect of corticosteroid treatment and enucleation on the visual prognosis of sympathetic ophthalmia. Am J Ophthalmol. 1983;96:290–4.
80. lubin JR, Albert, D.M. Sympathetic Ophthalmia (letter). Ophthalmology 1982;89:1291–2.

81. Levine MR, Pou CR, Lash RH. The 1998 Wendell Hughes Lecture. Evisceration: is sympathetic ophthalmia a concern in the new millennium? Ophthalmic Plast Reconstr Surg. 1999;15:4–8.
82. Migliori ME. Enucleation versus evisceration. Curr Opin Ophthalmol. 2002;13:298–302.
83. Zheng C, Wu AY. Enucleation versus evisceration in ocular trauma: a retrospective review and study of current literature. Orbit. 2013;32:356–61.
84. Yousuf SJ, Jones LS, Kidwell ED Jr. Enucleation and evisceration: 20 years of experience. Orbit. 2012;31:211–5.
85. Manandhar A. Sympathetic ophthalmia: enucleation or evisceration? Nepalese J Ophthalmol Biannual Peer-Rev Acad J Nepal Ophthalmic Soc NEPJOPH. 2011;3:181–7.
86. du Toit N, Motala MI, Richards J, Murray AD, Maitra S. The risk of sympathetic ophthalmia following evisceration for penetrating eye injuries at Groote Schuur Hospital. Br J Ophthalmol. 2008;92:61–3.
87. O'Donnell BA, Kersten R, McNab A, Rose G, Rosser P. Enucleation versus evisceration. Clin Exp Ophthalmol. 2005;33:5–9.
88. Gurdal C, Erdener U, Irkec M, Orhan M. Incidence of sympathetic ophthalmia after penetrating eye injury and choice of treatment. Ocular Immunol Inflamm. 2002;10:223–7.
89. Hebestreit H, Huppertz HI, Sold JE, Dammrich J. Steroid-pulse therapy may suppress inflammation in severe sympathetic ophthalmia. J Pediatr Ophthalmol Strabismus. 1997;34:124–6.
90. Kilmartin DJ, Forrester JV, Dick AD. Cyclosporin A therapy in refractory non-infectious childhood uveitis. Br J Ophthalmol. 1998;82:737–42.
91. Kilmartin DJ, Forrester JV, Dick AD. Cyclosporine-induced resolution of choroidal neovascularization associated with sympathetic ophthalmia. Arch Ophthalmol. 1998;116:249–50.
92. Yang CS, Liu JH. Chlorambucil therapy in sympathetic ophthalmia. Am J Ophthalmol. 1995; 119:482–8.
93. Tessler HH, Jennings T. High-dose short-term chlorambucil for intractable sympathetic ophthalmia and Behcet's disease. Br J Ophthalmol. 1990;74:353–7.
94. Goldstein DA, Fontanilla FA, Kaul S, Sahin O, Tessler HH. Long-term follow-up of patients treated with short-term high-dose chlorambucil for sight-threatening ocular inflammation. Ophthalmology. 2002;109:370–7.
95. Moore CE. Sympathetic ophthalmitis treated with azathioprine. Br J Ophthalmol. 1968;52:688–90.
96. Kim JB, Jeroudi A, Angeles-Han ST, Grossniklaus HE, Yeh S. Adalimumab for pediatric sympathetic ophthalmia. JAMA Ophthalmol. 2014; 132:1022–4.
97. Menghini M, Frimmel SA, Windisch R, Meier FM. Efficacy of infliximab therapy in two patients with sympathetic ophthalmia. Klin Monatsbl Augenheilkd. 2011;228:362–3.
98. Gupta SR, Phan IT, Suhler EB. Successful treatment of refractory sympathetic ophthalmia in a child with infliximab. Arch Ophthalmol. 2011;129:250–2.