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Sympathetic Ophthalmia: A Comprehensive Update

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ABSTRACT

Introduction: Although sympathetic ophthalmia (SO) rarely occurs, it is still considered as a harmful condition that requires early recognition and aggressive therapy to maintain or improve visual outcome.
Objective: This review aims to provide recent information regarding etiopathogenesis, clinical manifestation, diagnosis, and SO treatment as well.
Methodology: Articles were identified from databases using keywords combination of ("Sympathetic Ophthalmia" AND "Clinical Features" AND "Diagnosis" AND "Treatment").
Conclusion: SO is an underdiagnosed vision-injuring disease. Therefore, early detection and adequate treament of SO are needed as the main principle for successful SO management.

Keywords: Sympathetic ophthalmia, Clinical features, Diagnosis, Treatment

INTRODUCTION

Sympathetic ophthalmia (SO) is widely known due to its bilateral, widespread, granulomatous inflammation of the entire uvea. This condition mainly appears in any trauma or surgery-induced penetrating injury towards an eye (inciting eye)[1]. However, the injury may lead into inflammation in both eyes through sympathetic response. SO cases are rarely reported, with an occurrence of 0.2%–0.5% following eye penetrating injuries and 0.01%–0.05% after intraocular procedure[2]. The importance of knowing the possible deterioration of SO as a sight-threatening disease has to be highlighted, as one-third of SO patients ended up with visual acuity of 20/200 or worse, leading to an urgent need in prompt and aggressive anti-inflammatory therapy for visual outcomes improvement[3]. As such, this review provide recent information regarding etiopathogenesis, clinical manifestation, diagnosis, and SO treatment.

METHODOLOGY

Articles were identified from databases: PubMed, Science Direct, Google Scholar and Wiley Online Library. Researchers used a combination of keywords from Boolean operators, namely ("Sympathetic Ophthalmia" AND "Clinical Features" AND "Diagnosis" AND "Treatment"). The articles were selected based on: (1) The following topics included sympathetic ophthalmia clinical features, diagnosis, and treatment; (2) Published in last 10 years. The exclusion criteria used by researchers include (1) the topic of the article is not relevant to the study objectives (2) The article is not a full text; (3) The article is the result of proceedings or conferences.

Review

Epidemiology

As one of the rare ocular diseases, SO has been reported for its declining incidence recently. The occurrence is estimated in 0.02%-0.05% cases following ocular trauma, and in 0.01% cases post-ocular surgery as well. Furthermore, a prospective surveillance study from the United Kingdom confirmed an incidence of approximately 0.03/100,000 population/ year. Hence, ocular surgery is considered as more frequent cause of SO than traumatic ocular injury[4].

The onset of SO may appear anytime, ranging from days to decades following any ocular trauma or surgery. In most cases (80-90%), it develops within the first 3 months to a year, but there have been reports of it developing up to 66 years later. Study by Ozdemir et al. found that SO can manifest anytime from 15 days to 60 years after the triggering event. There has not been any precise theory regarding various time intervals in the development of SO[5].

It is expected that about 0.3% of uve it is cases are due to sympathetic ophthalmia (SO), as it occurs in 0.2% cases of non-surgical wounds, 0.19% from ocular penetrating injuries, and 0.007% from eye surgery. Furthermore, the prevalence of SO after pars plana vitrectomy is at 0.01%, while the prevalence increases to 0.06% after vitrectomy for penetrating injuries management.

Post-traumatic SO is 1.8 times more common in male due to occupational hazards and outdoor activities. Although, the proportion of postsurgical SO is equal for both male and female population. Recently, there has been an increasing incidence of post-surgical SO. Castiblanco et al. discovered that 44% cases were due to post-surgical trauma, in which 21% occurs post-parsplana vitrectomy[6].

Risk Factors and Pathophysiology

Any trauma or surgery-induced penetrating injury are the most frequent risk factor of SO. Vitreoretinal surgery, specifically pars plana vitrectomy, is considered as a leading factor of SO in current medical practice. As such, many researchers proposed that the future possibility of developing SO after pars plana vitrectomy procedure should be addressed, especially with its high estimated risk (1 in 799).

Few SO cases have also been linked with ocular blunt traumas, intraocular foreign body, along with chemical and thermal injuries. Some penetrating surgical interventions that is linked as SO trigger event, including cataract surgery, Intravitreal injection, iridencleisis, and iris/uveal inclusion in the wound. There are also other ocular surgical procedures as well, including transscleral cyclophoto-coagulation, scleral buckling, proton beam radiation, enucleation, penetrating keratoplasty, conjunctival flap procedure for perforated corneal ulcer, phakic intraocular lens implantation, evisceration, iridectomy, trabeculectomy, repair of cyclodialysis cleft, and paracentesis[6].

Up until today, the particular cause of SO remains unidentified, although it is discovered that uveal tissue prolapse after intraocular surgery or penetrating damage. Despite experiments that are conducted in animal models, it has been showed that the S antigen and the interphotoreceptor Retinoid-binding antigen induced a SO-resembling condition in monkeys. In a study conducted by Rao et al, it is proved that sample group with penetrating injury in anterior chamber exhibit local polymorphonuclear leucocytes reactions and similar histological features of sympathetic ophthalmia as well[7].

As the immune-privileged organ, eyes have an efficient lack of efferent lymphatics. With the extensive lymphatic drainage area at conjunctiva, antigens injected into the subconjunctival region will reach the closest lymph nodes. A similar process appeared when uveal antigens are exposed to lymphatic vessels during penetrating injury, leading to a uveal tissue prolapse[8].

Another theory of SO pathophysiology is autoimmune reaction. Any trauma or surgery-induced penetrating injury initiates

the first stage of an autoimmune response (the afferent phase). This may be due to the exposure of secreted ocular antigens to the immune system following trauma or an alteration of the immune tolerance to ocular antigens. The eye lacks of lymphatic system. After processing the antigen, APCs like macrophages or dendritic cells presents the antigen peptide to autoreactive CD4+ T-cells at lymph nodes or spleen via HLA II molecules. The T-cell receptor (TCR) identifies the antigen peptide, resulting in the stimulation of CD4+ cells, particularly Th1 cells. Th1 cell undergoes clonal expansion and migration. There are also endothelial alterations, cytokine milieu modification, along with activation of multiple effector pathways in the sympathizing eye[6].

Clinical Manifestation

A standardized classification criteria for SO are described from The Standardization of Uveitis Nomenclature Working Group (Table 1)[4].

The initial sign of SO in patients is asymmetric panuveitis, or a more severe inflammation of the originating eye. Such said, patients may experience various symptoms, such as reduced vision, ranging from slight visual impairment to severe visual loss, pain, redness, photophobia, photopsia, and floaters[6]. Historyiof trauma or ocular surgery should be taken[5].

Detailed ocular examination such as snellen visual acuity, slit-lamp examination, applanation tonometry, and dilated fundoscopy should be done. Anterior segment examination by slit lamp usually reveals mutton-fat keratic precipitates (KPs) on corneal endothel, cells and flare, and ciliary injection[5]. Iris thickening and sometimes iris nodules are visible. Posterior synechiae with weak dilating pupils are commonly observed[8].

Findings in the posterior segment from dilated funduscopy are divided based on its chronicity. During acute stage, patients may show multifocal retinochoroidal nodular lesions, choroidal thickening, vitritis, papillitis, and exudative retinal detachment. Meanwhile, chronic stage of SO shows subretinal fibrosis, optic and retinochoroidal atrophy, multiple yellow-white round subretinal lesions located in the mid-equatorial region (Dalen-Fuchs nodules), and sunset glow fundus [5].

Table 1: Classification criteria for sympathetic ophthalmia

1.	History of unilateral ocular trauma or surgery
	AND
2.	Ocular inflammation, either
	i. Bilateral ‘OR’
	ii. If there is no view in the inciting eye (e.g., enucleated, phthisis, opaque cornea), then detectable inflammation in the sympathizing eye
	AND
3.	Evidence of more that isolated anterior uveitis, either
	i. Anterior chamber and vitreous inflammation ‘OR’
	ii. Panuveitis with choroidal involvement
	Exclusion
1.	Positive serology for syphilis using a treponemal test
2.	Evidence for sarcoidosis (either bilateral hilar adenopathy on chest imaging or tissue biopsy demonstrating non-caseating granulomata)

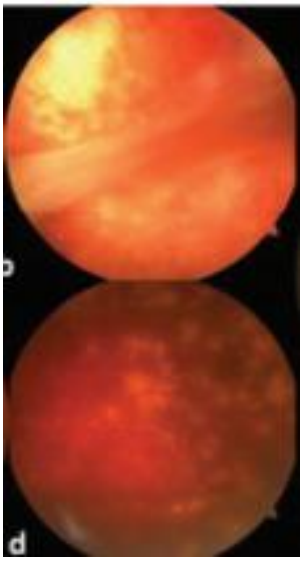

Figure 2. Fundus images of the sympathizing eye in the chronic stage showing sunset glow fundus and Dalen-Fuchsu(D-F)nodules[5]

Imaging

Several imaging modalities plays a supporting role in identifying SO, despite the diagnosis being clinical. Moreover, imaging modalities, such as fluorescein angiography, b-scan ultrasonography (USG), and optical coherence tomography (OCT), are also beneficial for monitoring the disease course and treatment response.

There are two different abnormal fundus fluorescein angiographic features that might be seen in SO as the initial presentation: small hyperfluorescent leak or multiple hypofluorescent spots with dye pooling in the late phase. The delay in choroid perfusion may occur locally or in patchy regions. Usually, there is evidence of optic disc vessel leaks, or staining of the nerve head[9].

The features observed from the second type of the angiographic similar to patients with acute posterior multifocal placoid pigment epitheliopathy (APMPPE). These alterations are infrequent and involving hypofluorescent spots of the initial stage of angiography, which then changed to hyperfluorescent spots. The hypofluorescence could result from choroidal fluorescence obstruction due to Dalen-Fuchs nodules or from the focal destruction of the choriocapillaris by choroid inflammatory cells[9].

B-scanEultrasonography in SO typically shows diffuse. choroidal thickening (ini>60% of cases), or in some cases, serous retinal detachment at the posterior pole. During OCT evaluation in overall disease course, SO shows unusual findings that is divided according to its phases. The acute phase reveals multiple serous detachment of the neurosensory retina, as well as the fluid accumulations in between the neurosensory retina and the underlying RPE. Moreover, longstanding fluid accumulation may result in an irreversible damage of the overlaying retina, leading to a cystoid macular edema formation and loss of photoreceptors function[9].

Choroidal atrophic changes may have been reported in the chronic stage. In this case, the spectral domain-OCT (SD-OCT) can also be used to identify and monitor the evolution of Dalen-Fuchs nodules, which appears as a round-shaped hyperreflective areas located at the level of the outeriretina, disrupting the RPE and the outer retinal bands[9].

Management

Although corticosteroids are considered as the first line treatment of SO, it may not be very effective as a prophylaxis. With such said, the administration of additional immunomodulator therapy during the initial presentation is much more recommended. Oral prednisone is initially administered at a high dosage of 1-2 mg/kg/day. Moreover, the administration of intravenous (IV) pulse methylprednisolone (steroid) at 1g/day for 3 days has been used for severe cases, followed by high-dose oral steroids from the fourth day. Additionally, oral proton pump inhibitors (PPIs) and calcium supplements should also be administered from the beginning.

The gradual progress of patient towards therapy are monitored by visual acuity, anterior segment examination, and funduscopy. OCT may also be helpful for supplemental objective monitoring, particularly in examining subretinal fluid, retinal detachment, and choroidal thickness.

To start immunomodulators therapy, patient has to be qualified for these indications: contraindication to steroid, significant steroid-induced side effects, flare-ups whileitapering or stopping of steroid, or inadequate response after steroid therapy[6]. Furthermore, the immunomodulatory treatment takes up to 18 months or more, with variousyagents, suchxas azathioprine, mycophenolate mofetil, cyclosporine and cyclophosphamide (Table 2)[8].

The local administration of intravitreal corticosteroid may be beneficial in reducing the systemic doses ofy steroids and other immunosuppressive agents, as it was found necessary to maintain remission with less systemic side effects to enables high concentrations of direct drug delivery[8]. Triamcinolone injection with intravitreal approach demonstrated decrease of intraocular inflammation, as well as improvement in the visual field andiuacuity with less doses of systemic therapy[9]. However, there are potential adverse effects that are linked with intravitreal steroid injections such as cataract, secondary glaucoma, retinal detachment, retinal tears, and endophthalmitis[6].

Surgical management is only considered if the exciting eye is blind or severel traumatized. The most common surgical procedure is evisceration or enucleation of the exciting eye. However, there are present debates regarding the most suitable procedure and the ideal surgical time, as the previous insight suggested that enucleation of injured eye within 2 weeks from injury onset might be considered as SO prevention[6]. This argument were supported by several studies which revealed visual improvement of sympathizing eye after early enucleation. On the contrary, another study showed no benefit of enucleation on the sympathizing eye at any time during the disease course[6].

Complications, such as choroidal neovascularization, chorioretinal and optic nerve atrophy, phthisis bulbi, and severe vision impairment, may happen if SO did not meet adequate management. Cataract and glaucoma may develop in SO patients due to chronic uveitis and the long-term use of topical and systemic corticosteroids[5].

Studies shows that adequate treatment with appropriate medication dose to control inflammation is crucial for enhancing the visual outcome of SO patients. According to Zhao etxioal., 72% patients experienced visual improvement after receiving aggressive and adequate treatment for SO, while 17% maintained their visual function and 9% experienced worsening vision compared to visual acuity prior to the study[2].

CONCLUSION

Despite being one of the underdiagnosed-rare eye diseases, SO is still considered as a harmful condition towards humans vision. Therefore, early detection and adequate treatment are crucial to improve visual prognosis. The SO management demands a thorough history taking, and a detailed ocular examination. Imaging modalities plays a supplemental role in diagnosing SO. Pharmacology intervention mainly consist of corticosteroid, although immunomodulatory agents could also be considered. Visual prognosis in SO patient may favorable depends on its treatment.

Declaration by Authors

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