Sympathetic Ophthalmia

ABSTRACT Sympathetic ophthalmia is a rare, bilateral granulomatous uveitis that occurs after either surgical or accidental trauma to one eye. The ocular inflammation in the fellow eye becomes apparent usually within 3 months after injury. Clinical presentation is an insidious or acute anterior uveitis with mutton-fat keratic precipitates. The posterior segment manifests moderate to severe vitritis, usually accompanied by multiple yellowish-white choroidal lesions. Evidence suggests that sympathetic ophthalmia represents an autoimmune inflammatory response against choroidal melanocytes mediated by T cells. Diagnosis is based on clinical findings and a history of previous ocular trauma or surgery. Other causes of granulomatous uveitis, such as Vogt-Koyanagi-Harada disease, sarcoidosis, tuberculosis, and syphilis should be considered. Treatment of sympathetic ophthalmia consists of systemic anti-inflammatory agents with high dose oral corticosteroid as the drug of choice. However, if the inflammation cannot be controlled, cyclosporine is then used. Other immunosuppressive agents, such as chlorambucil, cyclophosphamide or azathioprine, may be necessary for the control of inflammation. The role of enucleation after the diagnosis of sympathetic ophthalmia remains controversial. Visual prognosis is reasonably good with prompt wound repair and appropriate immunomodulatory therapy.

KEYWORDS review, ophthalmia, sympathetic, eye, diagnosis, therapy

INTRODUCTION

Sympathetic ophthalmia has been known since ancient times; however the first complete description of the disease dates back to the nineteenth century.1 In 1865, William Mackenzie described six patients, all of whom eventually became blind, who developed sympathetic ophthalmia following penetrating eye injury.2 Ernst Fuchs established this disease as a distinctive clinical entity in 1905 with his histological description of sympathetic ophthalmia.3

Sympathetic ophthalmia is a bilateral, diffuse granulomatous uveitis that occurs after trauma to one eye (exciting eye). Penetrating or surgical injury to the exciting eye can lead to an inflammatory response not only in the traumatized eye, but also in the fellow eye (sympathizing eye). The time from ocular injury to onset of sympathetic ophthalmia varies greatly, ranging from a few days to decades, with 80% of the cases occurring within 3 months after injury to the exciting eye4 and 90% within 1 year.5,6 Eye penetration is not essential for the development of sympathetic ophthalmia; non-perforating procedures, such as laser cyclotherapies,7 cyclophotocoagulation8 and proton beam irradiation for choroidal melanoma9 have been associated with the disease.
Given its rare occurrence, the true incidence of sympathetic ophthalmia is difficult to precisely establish. During the last 30 years, significant improvements in the management of ocular trauma combined with the advent of immunomodulatory therapy (including corticosteroids) and the use of antibiotics has lead to a dramatic decrease in the incidence of sympathetic ophthalmia. In the past, trauma was the most common precipitating event; however, ocular surgery is now considered the major risk factor, particularly vitreoretinal surgery. In 1982, Gass reported 0.01% prevalence of sympathetic ophthalmia following pars plana vitrectomy, and a 0.06% prevalence when there was a history of another penetrating wound. Better access to eye care following accidental trauma, combined with advances in microsurgical techniques resulting in an increase in the number of ocular surgeries, may be responsible for this change in the etiologic profile from penetrating injury to surgical trauma. In a recent report, sympathetic ophthalmia accounted for about 0.3% of the uveitis and its 1-year incidence was calculated to be a minimum of 0.03/100,000 population. There is no known gender or race predilection.

**Clinical Presentation**

Sympathetic ophthalmia presents as a bilateral diffuse uveitis. Patients report insidious onset of blurry vision, pain, epiphora, and photophobia in the sympathizing, non-injured eye. This is accompanied by conjunctival injection and a granulomatous anterior chamber reaction with mutton-fat keratic precipitates on the corneal endothelium. The iris may become thickened from lymphocytic infiltration; the severe inflammation may lead to formation of posterior synechiae. Intraocular pressure may be elevated secondary to inflammatory cell blockage of the trabecular meshwork, or it may be low as a result of ciliary body shutdown.

The posterior segment exam typically reveals a moderate to severe vitritis with characteristic posterior pole and mid-equatorial yellowish-white choroidal lesions, which may become confluent with time. These choroidal infiltrates correspond to the Dalen-Fuchs nodules seen on histopathological examination. Papillitis, peripapillary choroidal lesions and exudative retinal detachment may also occur (Figures 1A, B). The clinical presentation of sympathetic ophthalmia covers a wide spectrum depending on the severity of the disease (Table 1).

Complications of sympathetic ophthalmia include secondary glaucoma, cataract, and chronic maculopathy. Choroidal neovascularization, chorioretinal and optic atrophy, and phthisis bulbi are rare and are usually related to a delayed diagnosis and inappropriate treatment.

Sympathetic ophthalmia may present with extraocular findings similar to those observed with Vogt-Koyanagi-Harada disease (VKH), including cerebrospinal fluid pleocytosis, hearing disturbances, alopecia, poliosis and vitiligo. Though not commonly present, these findings reinforce the notion that sympathetic ophthalmia is a systemic disease requiring systemic therapy.

**Etiology**

The precise pathogenesis of sympathetic ophthalmia has not yet been clearly elucidated. In the original...
Ocular Findings in Sympathetic Ophthalmia

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description of the disease, MacKenzie postulated that the inflammatory process spreads from one eye to another via the optic nerve and optic chiasm. However, current evidence suggests a role for immune dysregulation as a primary etiological mechanism. There appears to be an autoimmune inflammatory response directed against ocular self-antigens found on choroidal melanocytes.

The histological features of sympathetic ophthalmia are similar in both the exciting and the sympathizing eye. Typically, there is a diffuse granulomatous, non-necrotizing inflammatory reaction with thickening of the posterior choroid secondary to infiltration with mononuclear and epithelioid cells. The choriocapillaris and retina are classically not involved in the inflammatory reaction; however, atypical features, such as retinal perivasculitis, retinitis, retinal detachment, gliosis as well as focal involvement of the choriocapillaris, have been described by several authors.

On histopathologic inspection, the yellowish-white choroidal lesions seen clinically correspond to collections of lymphocytes, histiocytes, and depigmented retinal pigment epithelial cells lying beneath Bruch’s membrane. Although present in one-third of patients with sympathetic ophthalmia, these Dalen-Fuchs nodules are not pathognomonic for the disease.

Immunopathologic studies suggest an early infiltration of CD4+ helper/inducer T cells, followed by an infiltration of CD8+ suppressor/cytotoxic T cells. These findings indicate that there is a dynamic cellular immune response, mediated predominantly by T cells, during the inflammatory process of sympathetic ophthalmia.

There is evidence suggesting that choroidal melanocytes may be an inciting target in developing sympathetic ophthalmia. Functional tests in vitro with peripheral blood of patients with sympathetic ophthalmia show T cell proliferative responses to uveal and uveoretinal extracts. In addition, the histological finding of selective loss of choroidal melanocytes and clinical similarities with VKH further support the role of these melanocytes as a possible trigger for the inflammatory response.

Sympathetic ophthalmia has been associated with particular major histocompatibility antigen (MHC) haplotypes, further suggesting a role for immune dysregulation in its pathogenesis. Patients with sympathetic ophthalmia are more likely to express human leukocyte antigen DR4 (HLA-DR4, and closely related HLA-DQw3 and HLA-DRw53) phenotype. These phenotypes are also found more frequently in patients with VKH. Therefore, in selected patients, there may be a genetically predisposing factor to developing sympathetic ophthalmia following accidental or surgical ocular trauma.

There has long been speculation that an infectious agent may be required for the development of sympathetic ophthalmia. However, no organism has ever been consistently isolated from eyes with sympathetic ophthalmia, and the disease has never been incited in animal models following injection of an infective agent. Nonetheless, through molecular mimicry of an endogenous ocular antigen, a bacterial antigen, rather than active proliferation of the organism, may be the inciting agent in the immune response.

Autoimmunity and cell-mediated immune mechanisms are considered to play a mediating role in pathogenesis of sympathetic ophthalmia. MHC molecules play an important regulatory function in the immune response by controlling the selection, degradation, and presentation of antigens within antigen presenting cells and their recognition by effector T cells. Current evidence suggests that in patients with sympathetic ophthalmia, there is an aberrant immune response to ocular self-antigens. Specific ocular antigens may interact with HLA-DR4 in a particular manner, triggering an inflammatory response directed primarily at the choroid. In a non-penetrated eye, immune privilege of the eye prevents ocular antigens from activating the immune system. However, trauma, either accidental or surgical, may expose ocular antigens in the exciting eye, initiating a systemic immune response that ultimately affects both eyes.

Differential Diagnosis

The differential diagnosis of sympathetic ophthalmia includes other causes of granulomatous uveitis...
The clinical presentation of sympathetic ophthalmia can be strikingly similar to VKH, often making the distinction between the two diagnoses difficult. Importantly, patients with VKH do not report a prior history of ocular injury; moreover, VKH patients usually present with systemic signs and symptoms, such as hearing dysfunction, skin changes, cerebrospinal fluid pleocytosis and meningeal signs, which are not classically associated with sympathetic ophthalmia. Sarcoidosis, tuberculosis and syphilis may also resemble sympathetic ophthalmia, but can be excluded after a comprehensive systemic workup.

It is important to rule out potentially devastating infections, such as fungal and bacterial infections, which may evolve rapidly from uveitis to severe endophthalmitis. Post-traumatic iridocyclitis may also cause an inflammatory reaction. However, neither infection nor iridocyclitis involves the fellow eye.

Other entities with features similar to sympathetic ophthalmia that should be considered in the differential diagnosis include multifocal choroiditis, lens-induced uveitis, acute posterior multifocal placoid pigment epitheliopathy, lymphoma and uveal effusion syndrome.

**DIAGNOSTIC WORKUP**

The diagnosis of sympathetic ophthalmia is based on history (with particular attention to penetrating ocular trauma) and clinical examination. There are no specific laboratory studies to establish the diagnosis of sympathetic ophthalmia; however, focused clinical testing can be used to rule out other disease entities that may have a similar clinical picture (Table 2).

**Laboratory Tests**

Lumbar puncture may be performed if the diagnosis is not clear; the presence of pleocytosis favors the diagnosis of VKH.27

Tuberculosis, sarcoidosis and syphilis are usually accompanied by constitutional signs and symptoms of the underlying systemic disease. These features, combined with appropriate testing for tuberculosis (PPD skin testing and chest radiograph), sarcoidosis (serum angiotensin-converting enzyme and lysozyme, and chest radiograph), and syphilis (RPR and FTA-ABS) can distinguish these systemic infections from sympathetic ophthalmia.

HLA typing may be helpful but is not essential in confirming the diagnosis of sympathetic ophthalmia.

**Ocular Tests**

Fluorescein angiography (FA) and indocyanine green angiography (ICGA) are useful adjuncts in establishing the extent and severity of sympathetic ophthalmia. In the acute phase, IVFA shows multiple hyperfluorescent

**TABLE 2** Differential Diagnosis of Sympathetic Ophthalmia

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areas early in the venous phase that then demonstrate late leakage (Figure 3). Early blocked fluorescence results from the Dalen-Fuchs nodules. Depending on the state of the overlying retinal pigment epithelium, the Dalen-Fuchs nodules may be either hyper- or hypofluorescent in IVFA. B-scan ultrasonography can also be useful to demonstrate the amount of choroidal thickening prior to treatment.

FIGURE 3 Fluorescein angiography of the acute phase of sympathetic ophthalmia showing multiple hyperfluorescent dots in the mid-periphery with some confluency anteriorly (Courtesy of Carlos Eduardo Hirata, Brazil).

FIGURE 4 Treatment of sympathetic ophthalmia.

TREATMENT

The treatment of sympathetic ophthalmia is primarily medical. The mainstay of treatment is systemic immunomodulatory therapy (Figure 4).

Corticosteroids

Systemic corticosteroids are the first line therapy for sympathetic ophthalmia. Treatment is initiated with high dosage oral prednisone (1.0 to 2.0 mg/kg/day). Adjunctive topical corticosteroids and cycloplegics are used to prevent synechia formation from the anterior chamber reaction. High-dose oral corticosteroids are maintained for a minimum of three months, after which the response to treatment is evaluated. The clinical criterion for response to therapy incorporates an appraisal of the inflammatory response, such as the degree of choroiditis and papillitis. If there is a significant decrease in inflammation, a slow taper of the oral corticosteroid may be initiated. The minimum dosing schedule required for the control of inflammation is usually at least a year.

In severe cases, intravenous pulse steroid therapy can be employed (methylprednisolone 1.0 g/day for 3 days), followed by oral prednisone. Since relapses are common during medication tapering, the dosage of corticosteroid must be maintained at a sufficient level or increased accordingly in order to completely control the ocular inflammation.
Cyclosporine

If patients fail to respond to corticosteroids or have intolerable side effects, cyclosporine can be used as a long-term immunomodulatory agent. Cyclosporine is usually started at a dose of 5 mg/kg/day and increased until the ocular inflammatory reaction is under control. Once the disease is in remission for at least 3 months, a slow taper (0.5 mg/kg/day every 1–2 months) of cyclosporine can be initiated and progressively substituted by low doses of corticosteroid. Since cyclosporin can be nephrotic, hepatotoxic, neurotoxic, as well as produce hyperglycemia and hypertension, patients must be closely monitored.

Other Immunosuppressive Agents

Alkylating agents, such as chlorambucil and cyclophosphamide, or antimetabolites like azathioprine may also be utilized if the inflammatory reaction cannot be adequately controlled with corticosteroids or cyclosporine. However, given the more powerful nature and less favorable side-effect profile of these agents, collaborative management with experienced physicians is advisable.

Surgical Treatment

Surgery prior to disease onset appears to play an important role in the prevention of sympathetic ophthalmia. It is generally accepted that prompt wound closure or enucleation should be performed within 2 weeks of the initial traumatic event and may, in theory, decrease the risk of sympathetic ophthalmia. If wound closure is not performed within 2 weeks, enucleation should only be considered if the injured eye is blind or painful, as there is the remote possibility that the injured eye may turn out to be the eye with better vision if sympathetic ophthalmia is not successfully treated. Moreover, late enucleation has not been shown to be beneficial in the management of sympathetic ophthalmia. Once the disease has begun, the treatment of choice is systemic immunomodulatory therapy.

PROGNOSIS

Easy access to eye care, prompt wound repair, and heightened awareness of sympathetic ophthalmia have all helped in improving the prognosis of sympathetic ophthalmia. With immediate and aggressive use of corticosteroids, backed by immunosuppressive therapy for the steroid non-responders, the visual prognosis for patients afflicted with sympathetic ophthalmia is now much more favorable. However, the relapsing nature and potential morbidity associated with sympathetic ophthalmia demands careful lifetime follow-up to ensure prompt treatment of potentially serious sequelae of chronic panuveitis.

REFERENCES


