

Sympathetic Ophthalmia

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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 cyclocryotherapy,⁸ and proton beam irradiation for choroidal melanoma⁹ have been associated with the disease.

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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 led to a dramatic decrease in the incidence of sympathetic ophthalmia.¹⁰ In the past, trauma was the most common precipitating event; however, ocular surgery is now considered the major risk factor, particularly vitreoretinal surgery.^{11,12} 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.¹³ 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 uveitis¹⁴ and its 1-year incidence was calculated to be a minimum of 0.03/100,000 population.¹² 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 disease¹⁵ (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

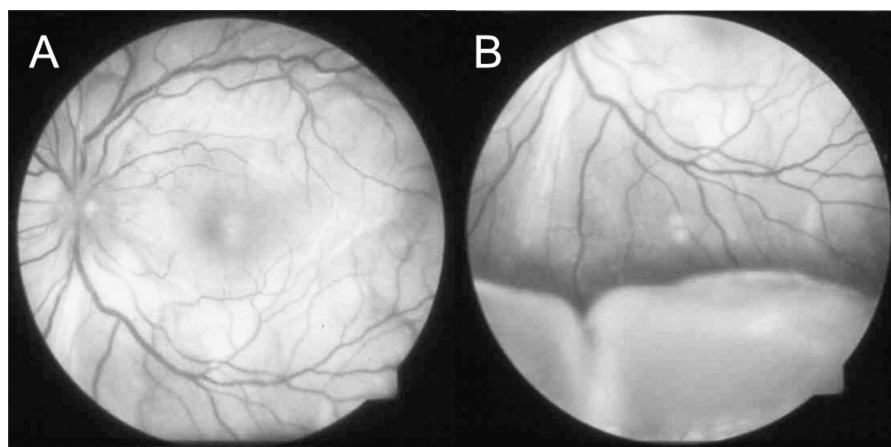


FIGURE 1 Clinical presentation of sympathetic ophthalmia: A. Diffuse choroiditis with papillitis, B. Exudative retinal detachment (Courtesy of Carlos Eduardo Hirata, Brazil).

TABLE 1 Ocular Findings in Sympathetic Ophthalmia

Ocular findings in sympathetic ophthalmia

History of ocular trauma or surgery
 Diffuse bilateral uveitis
 Mutton-fat keratic precipitates
 Vitritis
 Choroiditis
 Yellowish-white choroidal lesions
 Papillitis
 Exudative retinal detachment

description of the disease, MacKenzie postulated that the inflammatory process spreads from one eye to another via the optic nerve and optic chiasm.² 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;³ 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.^{5,16,17}

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,¹⁸ followed by an infiltration of CD8⁺ suppressor/cytotoxic T cells.¹⁹ These findings indicate that there is a dynamic cellular immune response, mediated predominantly by T cells, during the inflammatory process of sympathetic ophthalmia.¹⁸

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.^{20–22} 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.^{23,24} 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.²⁵ 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.²⁶

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

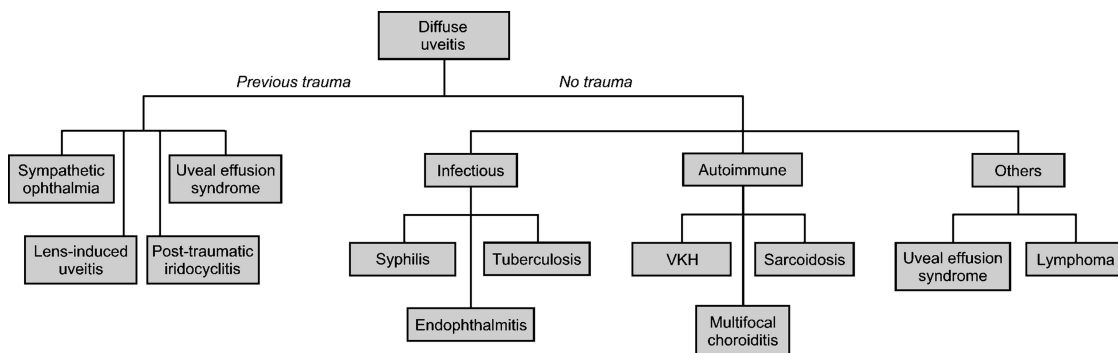


FIGURE 2 Differential diagnosis of sympathetic ophthalmia.

(Figure 2). 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

Diagnostic workup for sympathetic ophthalmia

History and clinical examination

Laboratory tests

CSF analysis

Tuberculosis

Sarcoidosis

Syphilis

HLA typing

Ocular tests

Fluorescein angiography

Indocyanine green angiography

B-scan ultrasonography

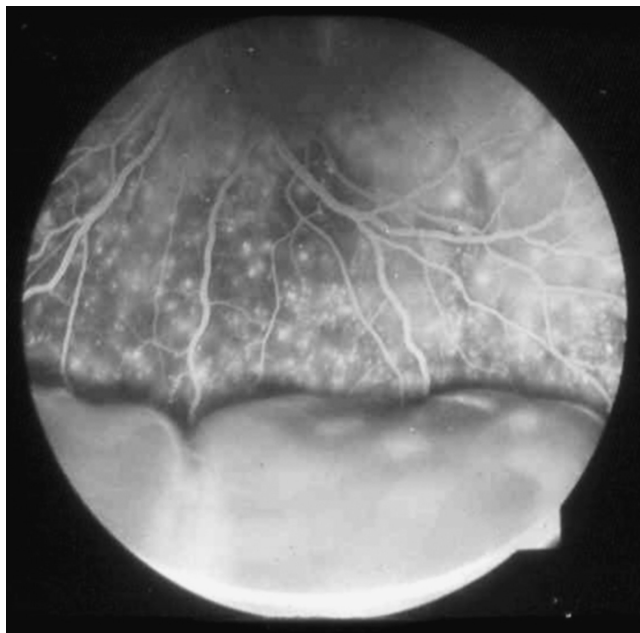


FIGURE 3 Fluorescein angiography of the acute phase of sympathetic ophthalmia showing multiple hyperfluorescent dots in the mid-periphery with some confluency anteriorly (Courtesy of Carlos Eduardo Hirata, Brazil).

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.

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 topic 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),²⁸ 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.

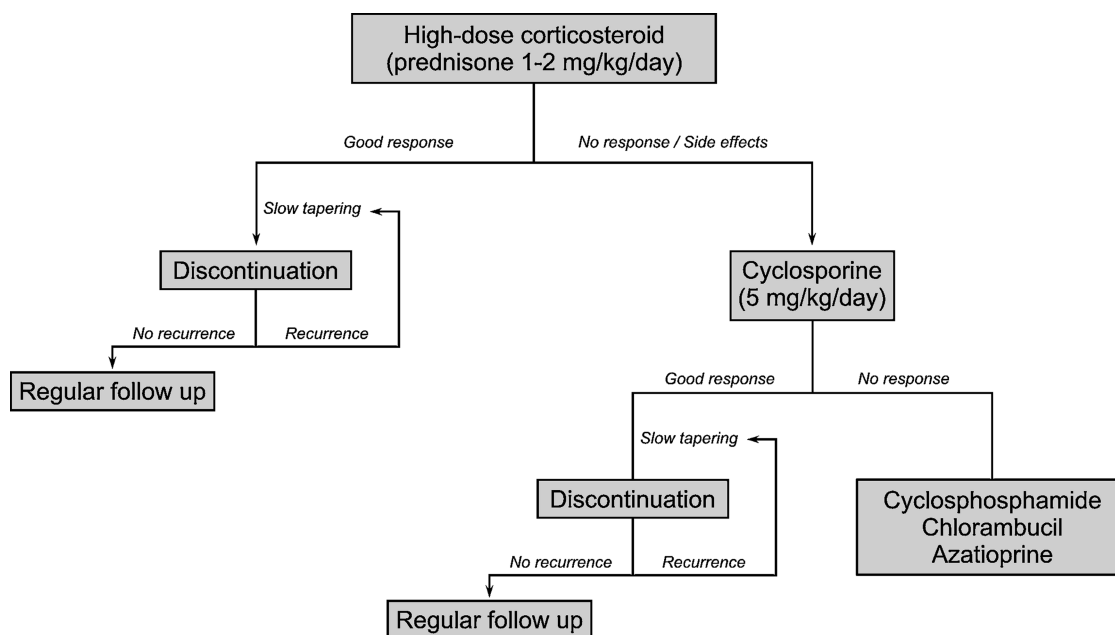


FIGURE 4 Treatment of sympathetic ophthalmia.

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 nephrotoxic, 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.^{5,29} 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

- [1] Albert DM, Diaz-Rohena R. A historical review of sympathetic ophthalmia and its epidemiology. *Surv Ophthalmol* 1989; 34:1–14.
- [2] MacKenzie W. *A Practical Treatise on Diseases of the Eye*, 3rd ed. London: Longmans, 1840.
- [3] Fuchs E. On sympathetic inflammation (initially remarks on serous iritis). *Graefes Arch Clin Exp Ophthalmol* 1905; 61:365–456.
- [4] Marak GE Jr. Recent advances in sympathetic ophthalmia. *Surv Ophthalmol* 1979; 24:141–56.
- [5] 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.
- [6] Goto H, Rao NA. Sympathetic ophthalmia and Vogt-Koyanagi-Harada syndrome. *Int Ophthalmol Clin* 1990; 30:279–85.
- [7] Singh G. Sympathetic ophthalmia after Nd:YAG cyclotherapy. *Ophthalmology* 1993; 100:798–9.
- [8] Biswas J, Fogla R. Sympathetic ophthalmia following cyclocryotherapy with histopathologic correlation. *Ophthalmic Surg Lasers* 1996; 27:1035–8.
- [9] Margo CE, Pautler SE. Granulomatous uveitis after treatment of a choroidal melanoma with proton-beam irradiation. *Retina* 1990; 10:140–3.
- [10] Power WJ. Sympathetic ophthalmia. In: Foster CS, Vitale AT, editors. *Diagnosis and Treatment of Uveitis*. Philadelphia: W.B. Saunders Company, 2002; 742–7.
- [11] Kilmartin DJ, Dick AD, Forrester JV. Sympathetic ophthalmia risk following vitrectomy: should we counsel patients? *Br J Ophthalmol* 2000; 84:448–9.
- [12] 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.
- [13] Gass JD. Sympathetic ophthalmia following vitrectomy. *Am J Ophthalmol* 1982; 93:552–8.
- [14] Gomi CF, Makdissi FF, Yamamoto JH, Olivalves E. [An epidemiologic study on uveitis.] *Rev Med (São Paulo)* 1997; 76:101–8.
- [15] Chan CC, Nussenblatt RB, Fujikawa LS, Palestine AG, Stevens G Jr, Parver LM, Luckenbach MW, Kuwabara T. Sympathetic ophthalmia. Immunopathological findings. *Ophthalmology* 1986; 93:690–5.
- [16] 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.
- [17] Winter FC. Sympathetic uveitis; a clinical and pathologic study of the visual result. *Am J Ophthalmol* 1955; 39:340–7.
- [18] Chan CC, Benezra D, Rodrigues MM, Palestine AG, Hsu SM, Murphree AL, Nussenblatt RB. Immunohistochemistry and electron microscopy of choroidal infiltrates and Dalen-Fuchs nodules in sympathetic ophthalmia. *Ophthalmology* 1985; 92:580–90.
- [19] Jakobiec FA, Marboe CC, Knowles DM 2nd, Iwamoto T, Harrison W, Chang S, Coleman DJ. Human sympathetic ophthalmia. An analysis of the inflammatory infiltrate by hybridoma-monoclonal antibodies, immunochemistry, and correlative electron microscopy. *Ophthalmology* 1983; 90:76–95.
- [20] Hammer H. Lymphocyte transformation test in sympathetic ophthalmitis and the Vogt-Koyanagi-Harada syndrome. *Br J Ophthalmol* 1971; 55:850–2.

- [21] Wong VG, Anderson R, O'Brien PJ. Sympathetic ophthalmia and lymphocyte transformation. *Am J Ophthalmol* 1971; 72:960–6.
- [22] Marak GE Jr, Font RL, Johnson MC, Alepa FP. Lymphocyte-stimulating activity of ocular tissues in sympathetic ophthalmia. *Invest Ophthalmol* 1971; 10:770–4.
- [23] Davis JL, Mittal KK, Freidlin V, Mellow SR, Optican DC, Palestine AG, Nussenblatt RB. HLA associations and ancestry in Vogt-Koyanagi-Harada disease and sympathetic ophthalmia. *Ophthalmology* 1990; 97:1137–42.
- [24] Kilmartin DJ, Wilson D, Liversidge J, Dick AD, Bruce J, Acheson RW, Urbaniak SJ, Forrester JV. Immunogenetics and clinical phenotype of sympathetic ophthalmia in British and Irish patients. *Br J Ophthalmol* 2001; 85:281–6.
- [25] Joy HH. Sympathetic ophthalmia. *Am J Ophthalmol* 1953; 36:1100–20.
- [26] Boyd SR, Young S, Lightman S. Immunopathology of the noninfectious posterior and intermediate uveitides. *Surv Ophthalmol* 2001; 46:209–33.
- [27] Ohno S, Minakawa R, Matsuda H. Clinical studies of Vogt-Koyanagi-Harada's disease. *Jpn J Ophthalmol* 1988; 32:334–43.
- [28] 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.
- [29] 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.