

Twenty cases of sympathetic ophthalmia

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SUMMARY We reviewed the charts of 20 patients with sympathetic ophthalmia who were seen in the uveitis clinic at the Eye and Ear Infirmary within an 11-year period. Of these 20 patients 14 maintained 20/50 or better visual acuity in at least one eye. We found early enucleation to be associated with a better visual prognosis, possibly due to earlier diagnosis and faster, more aggressive therapy rather than a reduction in antigenic load. The clinical appearance of Dalen-Fuchs nodules appears to indicate a more severe stage of disease. Chlorambucil was useful in patients with severe disease. To be effective and to lessen its side effects chlorambucil was given in daily dosages that were increased weekly over a short period to achieve bone marrow suppression. After a course of chlorambucil therapy intraocular inflammation could be controlled with topical steroids alone.

Sympathetic ophthalmia is a rare bilateral uveitis that can occur within a variable period of time after a penetrating injury or manipulation of the eye. We review 20 cases of sympathetic ophthalmia and contrast our clinical experience with that reported in the literature. We were specifically interested in finding out whether there were diagnostic clues for severity and whether we could elicit a better treatment regimen from previous results.

Methods and materials

We reviewed the charts of patients with sympathetic ophthalmia seen in the uveitis clinic at the Illinois Eye and Ear Infirmary from 1974 to 1985. Each patient's subsequent progress was determined, whenever possible, by telephoning the referring physician. Nine patients were followed up to the present time, three patients were followed up to their death, and three patients were seen for one, three, and five years. Five patients were seen for the referral visit only. Visual acuity, onset of injury and of sympathetic ophthalmia, time of enucleation if performed, and treatment regimen were recorded. The severity

of the sympathetic ophthalmia was rated as follows: the inflammation was defined as mild if it could be controlled with topical steroids or moderate if it could be managed with systemic steroids. The inflammation was considered severe if it could not be controlled with systemic steroids or if the corticosteroids could not be tapered without exacerbating the inflammation.

Fundus lesions thought to be clinically compatible with the histopathological Dalen-Fuchs nodule (granuloma) were noted. These white lesions were termed Dalen-Fuchs nodules if they were 1/10 disc diameter or less in size. The lesions had discrete hard edges and often looked like 'pin pricks' at the level of the retinal pigment epithelium (RPE). They resembled tiny hard drusen. When active, the Dalen-Fuchs nodules appear to have substance and when inactive appear as depigmented tiny spots.

For patients who had had several operations the period between the last operation and the onset of sympathetic ophthalmia was considered to be the interval between the inciting injury and the onset of symptoms. Patient 16 was excluded from the analysis of intervals because the date of onset of sympathetic ophthalmia was not known.

Chlorambucil was given to patients with severe disease after they were informed of its potential side

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effects. The initial dosage was 2 mg/day orally, which was increased by 2 mg/day each week. Prednisone dosage was concurrently reduced to zero with therapeutic response or stabilisation. Platelet and white blood cell counts were monitored weekly. When the platelet count was below $100 \times 10^9/l$ and/or the white blood cell count was below $2.8 \times 10^9/l$, chlorambucil therapy was discontinued.

Results

The 20 cases included in our study are shown in Table 1. They represented about 1.4% of the total number of referred uveitis patients seen at the Eye and Ear Infirmary. Five patients had mild disease, nine had moderate disease, and six had severe disease. Symptoms developed in seven patients within 12 weeks of the injury, in four within three to six months of the injury, and in eight more than six months after injury. Although patient 15 showed symptoms several days after the injury, this time interval could not be defined more precisely. The shortest documented time interval was four weeks and the longest 56 years. Eleven patients had additional procedures besides the original repair in the exciting eye before the onset of sympathetic ophthalmia (Table 1).

Fourteen of 20 patients maintained 20/50 or better visual acuity in at least one eye (Table 1). There was no great difference in the visual prognosis whether the patient had mild, moderate, or severe disease. Four of five patients with mild disease, six of nine patients with moderate disease, and four of six patients with severe disease maintained a visual acuity of 20/50 or better.

Nine patients underwent enucleation of the exciting eye. In five patients enucleation was performed within two weeks of the onset of symptoms (range, 4 to 11 days; mean, 6.6 days; Table 2). Four of these patients with early enucleations had final visual acuities ranging from 20/20 to 20/40, and the fifth (no. 5) had a severe cataract and 20/100 visual acuity. Three of these five patients who underwent early enucleation had severe disease.

The three patients whose eyes were enucleated after two weeks from the onset of symptoms (range, 5 to 20 weeks; mean, 13.7 weeks) had visual acuities of 20/50, counting fingers, and hand motion. Two of these patients had moderate disease, and one had mild disease. An additional patient (no. 17) underwent enucleation before the onset of symptoms and had 20/200 visual acuity.

Dalen-Fuchs nodules were seen in one of the six patients with mild disease, in two of nine patients with moderate disease, and in all six patients with severe disease.

We give an illustrative case report of severe

sympathetic ophthalmia that was treated with chlorambucil.

CASE REPORT

On 27 August 1978 a 6-year-old white girl sustained a penetrating corneal laceration with prolapsing lens and vitreous. The wound was repaired within five hours of the injury. Following the injury the visual acuity in the right eye was hand motion. On 23 September the anterior chamber in the right eye was flat and the retina was totally detached. In the left eye an iritis with keratic precipitates, 4+ flare with fibrinous strands and 3-4+ cells with 340° of posterior synechiae were present. The left fundus was normal except for a hyperaemic disc. Because the retinal detachment was believed to be unreparable, the right eye was enucleated on 27 September 1978. Histopathological examination showed sympathetic ophthalmia.

The patient was put on a regimen of oral prednisone, 60 mg/day, for several weeks. The fibrin in her anterior chamber disappeared, but 3+ flare and 3+ cells remained. On 12 October 1978 her visual acuity decreased to 20/40, and she was cushingoid. The prednisone was tapered to 80 mg every other day. On 2 November pigment clumping in the macula and several Dalen-Fuchs nodules were seen in the peripheral retina. Since the fundal lesions developed in spite of the high-dose therapy, she was initially given 2 mg of chlorambucil daily (Fig. 1), as described. By late December her white blood cell and platelet counts decreased to 3.5 and $90 \times 10^9/l$ respectively, and the anterior chamber inflammation subsided. At this time she was taking 10 mg of chlorambucil daily. By 4 January 1979 chlorambucil and the remaining small dose of prednisone were discontinued. The total dose of chlorambucil was 518 mg. For the next month topical steroids were used to control her inflammation and then were also discontinued. She has had no recurrence of the inflammation after seven years, and her visual acuity is 20/25.

The concurrent improvement in ocular inflammation and depression of white blood cell count occurred in patients 17, 19, and 20 also.

Discussion

According to Duke-Elder 80% of sympathetic ophthalmia cases occur within three months of the injury.¹ In our small series the incidence was 40% during that time period, possibly because we see only referred patients in our clinic. Such cases tend to be more complicated and may represent more atypical cases of sympathetic ophthalmia.

An interesting finding in our review is that the clinical presence of Dalen-Fuchs nodules appeared to

Table 1 Clinical data of patients with sympathetic ophthalmia

Case No	Age at injury (yr), race, sex	Injury	Signs and symptoms of sympathetic ophthalmia (interval from last surgery to inflammation)	Enucleation	Therapy	Visual acuity		Sympathetic ophthalmia interval from onset to last observation
						OD	OS	
<i>Mild cases</i>								
1	71 Oriental man	9/77 extracapsular cataract extraction OD with vitreous loss, intraocular steroid injection, 2 vitrectomies	16/3/79 3-week history of diminished visual acuity (2 yrs 7 mo)	29/3/79 OD	Topical steroids	E	20/50	4 yr
2	60 white man	5/78 extracapsular cataract extraction OS, severe phacoanaphylaxis, lens nucleus into posterior chamber; 6/78 vitrectomy OS	9/78 anterior chamber inflammation; Dalen-Fuchs nodules (3 mo)	—	Topical steroids ×6 mo	20/30	20/40	6 mo
3	26 white man	7/78 OD corneoscleral laceration	9/78 anterior chamber inflammation (2 mo)	—	Topical steroids	LP	20/50	1 mo
4	17 black man	6/78 OD corneal laceration; sector iridectomy several days later; 8/78 choroidal effusions drained; 4/80 penetrating keratoplasty OD	6/80 anterior chamber inflammation; depigmented areas in retina (2 mo)	—	Topical steroids	HM	20/20	5 yr
5	58 white man	9/12/81 globe perforation with retrobulbar injection OS; 11/12/81 perforation sutured; 18/12/81 vitrectomy	24/1/83 anterior chamber inflammation (13 mo)	28/1/83 OS	Topical steroids	E	20/100 (cataract)	4 yr
<i>Moderate cases</i>								
6	12 Hispanic boy	foreign body injury OD	2/74 2-month history pain, blurry vision (56 yr)	10/5/74 OD	Topical/systemic steroids	E	CF 1.5m	3 mo
7	38 Hispanic man	1948 struck in OD; 10/74 traumatic cataract removed	20/12/74 anterior chamber inflammation; 2-day history decreased visual acuity OS (2 mo)	26/12/74 OD	Topical/systemic steroids	E	20/20	1 yr
8	50 white man	1960 cataract extraction OD, 3 days later, extraction OS; third day after surgery, trauma OS	3-4 weeks later anterior chamber inflammation (3-4 wk)	—	Topical/systemic steroids	20/300	LP	13 yr
9	9 black boy	traumatic cataract OS; 6 months later; cataract extraction	11/82 anterior chamber inflammation; Dalen-Fuchs nodules (20 yr)	—	Topical/systemic steroids	20/20	NLP	3 yr
10	72 black man	no history of trauma; 1972 OD cataract; 1974 unrepairable retinal detachment OS	2/79 decreased visual acuity OD (7 yr)	6/79 OS	Topical/systemic steroids	HM	E	2 yr
11	28 black man	10/79 penetrating injury OS; repair delayed 2 weeks	12/79 anterior chamber and posterior inflammation (2 mo)	—	Topical/systemic steroid	20/25	20/40	*
12	9 white boy	1982 bottle rocket injury OD (no perforation noted, but eye not explored)	11/85 anterior chamber inflammation; Dalen-Fuchs nodules (3 yr)	—	Topical/systemic steroids	20/200	20/20	*
13	9 Hispanic girl	5/84 stuck OS; total hyphaema washed out; 10 days later, wound dehiscence	6/84 anterior chamber inflammation (1 mo)	—	Topical/systemic steroids	HM	20/20	1 yr
14	6 white boy	24/4/85 corneal laceration OS; flat anterior chamber	2/7/85 anterior chamber inflammation; Dalen-Fuchs nodules (3 mo)	—	Topical/systemic steroids	20/25	20/40	10 mo
<i>Severe cases</i>								
15	10 white boy	23/2/75 bullet wound OS	Several days later, anterior chamber inflammation; Dalen-Fuchs nodules (less than 14 days)	1/3/75 OS	Topical/systemic steroids; cyclophosphamide; chlorambucil	20/40	E	5 yr

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Table 1 Clinical data of patients with sympathetic ophthalmia—continued

Case No	Age at injury (yr), race, sex	Injury	Signs and symptoms of sympathetic ophthalmia (interval from last surgery to inflammation)	Enucleation	Therapy	Visual acuity		Sympathetic ophthalmia interval from onset to last observation
						OD	OS	
16	36 white man	9/75 corneoscleral laceration; 3 mo later vitrectomy, scleral buckle; iridectomy; lensectomy	Date? visual acuity and fields diminished; Dalen-Fuchs nodules (unknown)	2/76 OS	Systemic steroids; chlorambucil	20/40	E	2 yr
17	13 girl from India	28/1/82 perforated globe OD	6/82 Dalen-Fuchs nodules; retinal pigment epithelial changes; subretinal neovascularisation (5 mo)	20/2/82 OD	Topical/systemic steroids; azathioprine; chlorambucil	E	20/200	4 yr
18	6 white girl	27/8/78 corneal laceration OD	23/9/78 anterior chamber inflammation (Dalen-Fuchs nodules later during therapy) (1 mo)	27/9/78 OD	Topical/systemic steroids; chlorambucil	E	20/25	1 yr
19	56 white man	12/82 cataract extraction; 2/83, 9/83 retinal detachment repairs OD; 9/83 OD, 11/83 OS vitrectomy	7/83 vitritis; 1/84 Dalen-Fuchs nodules; bilateral subretinal neovascularisation (5 mo)	—	Topical/systemic steroids; chlorambucil	1/200	20/200	2½ yr
20	25 Hispanic woman	6/81 corneal laceration with iris prolapse	28/3/85 blurred vision; Dalen-Fuchs nodules; serous elevations of the retina (4 yr)	8-4-85 OD	Topical/systemic steroids; chlorambucil	E	20/20	1 yr

Abbreviations: OD indicates right eye; OS left eye; CF, count fingers; HM, hand motion; LP, light perception; NLP, no light perception; and E, enucleation. *Seen only once at initial presentation.

correlate with the severity of the disease. (See 'Materials and methods' for clinical definition of Dalen-Fuchs nodule). In our series one patient with mild disease, a few patients with moderate disease, and all the patients with severe disease had Dalen-Fuchs nodules. Histological studies support this concept. Dalen-Fuchs nodules stained with monoclonal antibody to specific lymphocyte receptors show histiocytes and suppressor/cytotoxic T cells.² Jakobiec and coworkers suggest that these T cells might be activated cytotoxic effector T cells.² Some cells in the Dalen-Fuchs nodules are thought to be transformed retinal pigment epithelial cells.³ If it is shown that Dalen-Fuchs nodules represent areas of autoimmune activity, it is not surprising that their appearance correlates with severity of disease.

Enucleation within two weeks of the onset of sympathetic ophthalmia has been associated with a better visual outcome and has been advocated by some investigators.^{4,5} Others believe that enucleation of an exciting eye after the onset of sympathetic ophthalmia has no effect.⁶ Our data support the finding that early enucleation results in a better visual

prognosis. However, patients who underwent early enucleation generally had more severe clinical disease by our criteria. Early enucleation may be associated with earlier diagnosis and quicker, more aggressive treatment. We recommend that a patient with sympathetic ophthalmia who has an exciting eye with no or bare light perception should undergo enucleation, since it may offer some therapeutic benefit. Moreover, histopathological examination can confirm a clinical diagnosis. We do not advocate enucleating eyes with useful vision.

As illustrated in our case report, we have found chlorambucil dramatically to reverse the course of sympathetic ophthalmia in four patients. This subsidence of inflammation coincides with a decreased white blood cell count, after which all medications are discontinued or only topical steroids are needed to control the inflammation. The other three patients (17, 19, and 20) we treated with chlorambucil also showed this relationship.

Previous authors, using chlorambucil to treat uveitis patients unresponsive to systemic corticosteroids, did not always find this relationship between

Table 2 Enucleation interval, disease severity, and final visual outcome*

Patient no	Enucleation interval	Disease severity	Final visual acuity
<i>Enucleation less than 2 weeks</i>			
5	4 days	Mild	20/100†
7	6 days	Moderate	20/20
15	8 days	Severe	20/40
18	4 days	Severe	20/20
20	11 days	Severe	20/20
<i>Enucleation greater than 2 weeks</i>			
1	5 weeks	Mild	20/50
6	3 months	Moderate	CF‡
10	4 months	Moderate	HM‡

* Patient 16 was not included owing to insufficient information. Patient 17 was not included because enucleation preceded the onset of sympathetic ophthalmia.

†Patient 5 developed a cataract in this eye.

‡CF=count fingers. HM=hand motion.

white blood cell suppression and therapeutic response.⁷ This difference between the two studies may be explained by how the corticosteroids were reduced. We may have tapered the steroids more aggressively than did the other investigators. Our goal was to have the patients taking only chlorambucil. The actions of chlorambucil and prednisone could presumably be additive and induce a therapeutic response before chlorambucil caused bone marrow depression. In addition, prednisone can produce peripheral leucocytosis, which may mask a suppression of white blood cell production.

Chlorambucil immunosuppressive therapy has been associated with several major complications, but these may be averted if the total chlorambucil dose remains low. The development of normal male secondary sexual characteristics is not affected, and sperm counts remain in the normal range if the total chlorambucil dose is below 8.2 mg/kg⁸ and 6.1 mg/kg,⁹ respectively. Tabbara found azoospermia and oligospermia in 10 male patients with Behçet's disease treated with a total chlorambucil dose greater than 10 mg/kg.¹⁰ Recovery of spermatogenesis has been noted about three years after the discontinuation of low or high dose chlorambucil therapy.¹¹ Development of female secondary sexual characteristics and fertility appears to be unaffected by chlorambucil therapy.^{8,12} Chlorambucil is a teratogen,^{13,14} and its ability to damage chromosomes¹⁵ probably means that chlorambucil is also a mutagen. However, except for one 7-year-old girl who contracted acute leukaemia after receiving a total chlorambucil dose of 300 mg (15 mg/kg)¹⁶ acute leukaemia does not occur in patients treated with a total dose of less than 1 g.¹⁷

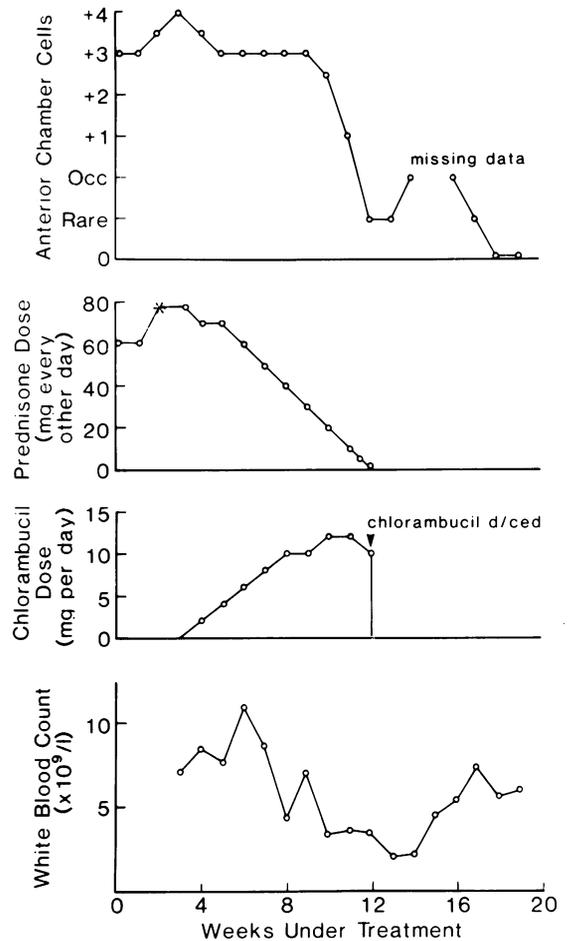


Fig. 1 The anterior chamber inflammation diminishes concurrently with the white cell suppression as a result of drug therapy in patient 18. Occ indicates occasional cell; rare, rare cell. *80 mg alternated with 20 mg daily.

Infections, particularly herpes zoster, develop in patients who tend to be on prolonged chlorambucil therapy.¹⁸ None of our four patients had any of the complications mentioned, though evaluations of fertility were not determined.

We believe that chlorambucil should be administered in progressively larger dosages. By increasing the daily dose weekly, bone marrow depression is achieved earlier, thus eliminating the ocular inflammation sooner and allowing a more rapid withdrawal of systemic steroids. This is important if the patient is experiencing severe side effects from the steroids. Moreover, a rapid induction of bone marrow depression limits the total chlorambucil dose and, as discussed, the incidence of complications from the

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chlorambucil therapy. However, weekly platelet and white blood cell counts are imperative. Chlorambucil immunosuppressive therapy has caused irreversible bone marrow failure.¹⁹

Cyclosporin, another immunosuppressive agent, has been recently used to treat uveitis.²⁰⁻²³ In one study nine patients with refractory posterior uveitis were administered systemic cyclosporin. All patients had an improved visual acuity, a reduced steroid dose, and decreased inflammation. However, in seven patients cyclosporin-induced renal toxicity necessitated a reduction in the cyclosporin dose, which led to a relapse of the uveitis.²⁰ Others have reported that the cyclosporin dose was tapered because of nephrotoxicity and that systemic corticosteroids had to be added to suppress the inflammation.²⁴ This experience indicates that clinically cyclosporin suppresses but does not eradicate ocular inflammation. Thus patients with severe uveitis would need chronic cyclosporin therapy, which has been associated with renal toxicity²⁵ and lymphoma.²⁶ This is different from our experience with chlorambucil, in which only short-term therapy was required.

The authors were supported in part by training grant 7038 and core grant 1792 from the National Eye Institute, Bethesda, Md, and by an unrestricted research grant from Research to Prevent Blindness, Inc, New York.

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Accepted for publication 19 January 1988.