

## CASE PRESENTATION

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A 31 year old female was referred in January 1998. The patient complained of floaters in both eyes.

### History of Illness:

The patient noted floaters in her right eye in March 1997 and was diagnosed as having posterior uveitis with perivenous sheathing in her right eye by her primary ophthalmologist. The left eye was found to be completely normal at that time. **Work-up** was initiated in March 1997. Results were as follows:

<b>Chest X-ray:</b>	<i>Normal</i>
<b>ANA:</b>	<i>Negative</i>
<b>Anti dsDNA:</b>	<i>Negative</i>
<b>RF:</b>	<i>Negative</i>
<b>CRP:</b>	<i>WNL</i>
<b>C3 and C4:</b>	<i>WNL</i>
<b><math>\alpha</math>-1 antitrypsin:</b>	<i>WNL</i>
<b>ESR:</b>	<i>5 mm/hr</i>
<b>HIV:</b>	<i>Not detected</i>
<b>Lyme serology:</b>	<i>Negative</i>
<b>RPR:</b>	<i>Nonreactive</i>
<b>PPD:</b>	<i>Negative</i>

The patient was diagnosed as having idiopathic panuveitis in July 1997; there was also early disease in her left eye during that time. Prednisone 40 mg/day and topical Pred Forte QID OD was begun, but the patient could not tolerate systemic corticosteroids.

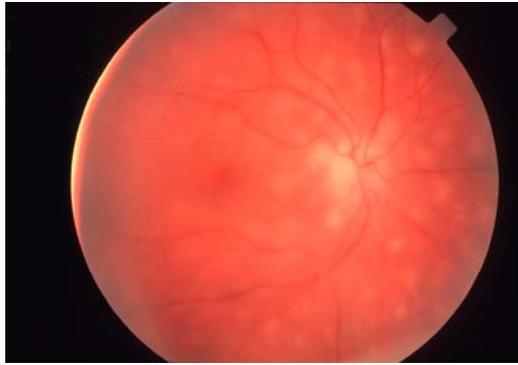
Her past medical history was unremarkable for diabetes, hypertension, arthritis, skin lesions and/or oral ulcers.

The patient had no family history of ocular disease with the exception of cataract in her grandmother.

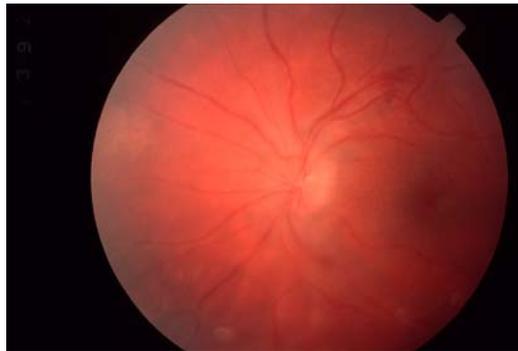
### Ocular Examination:

The patients' visual acuities were 20/20<sup>-1</sup> OU. Pupils showed no RAPD. Extraocular motility was full in both eyes. Intraocular pressure was 17 mmHg (applanation tonometry) OU. Biomicroscopic findings were normal in both eyes with the exception of 1+ vitreous cells OD and 1-2+ vitreous cells OS.

Ophthalmoscopy after dilation of the pupils revealed slightly blurry optic disc border OD and slightly blurry optic disc border nasally OS along with RPE changes of the macula in both eyes. Deep hypopigmented lesions were noticed around the optic disc and along the infero- and superotemporal vascular arcades in the right eye and nasal to the optic disc in the left eye. The left fundus also showed intraretinal hemorrhages along the superotemporal vascular arcade in the left eye. Retinal vessels showed some sheathing in both eyes. There was vitreous debris in the right eye. Peripheral retinal examination was negative for snowbanking in both eyes.



Fundus OD (January 1998)



Fundus OS (January 1998)



Fundus OS (January 1998)

The **initial impression** was;

Choroiditis in both eyes, more prominent in the right eye.

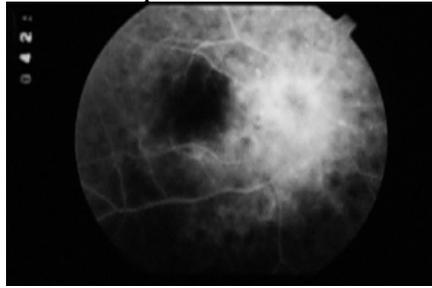
The plan was to evaluate for HLA typing in particular for HLA-A29, ACE, ANCA and FTA-ABS and to obtain a fluorescein angiogram (FA).

The **differential diagnosis** included:

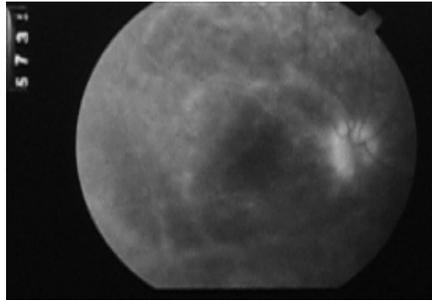
- Birdshot retinochoroidopathy (BSRC)
- Sarcoidosis
- Systemic Lupus Erythematosus
- Infectious causes: - Syphilis  
- Lyme disease

The **fluorescein angiogram** revealed patchy choroidal filling with delay of filling of the inferior retinal arteriols in both eyes. There was focal staining of retinal venule walls.

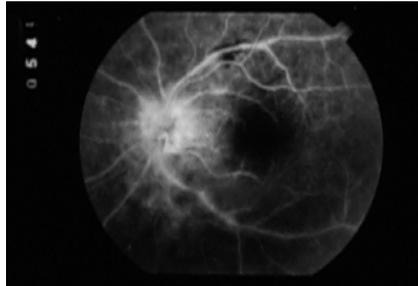
Multiple hypofluorescent spots that did not show hyperfluorescence or staining in late phases of the angiogram and leakage from the optic discs in late frames was also evident.



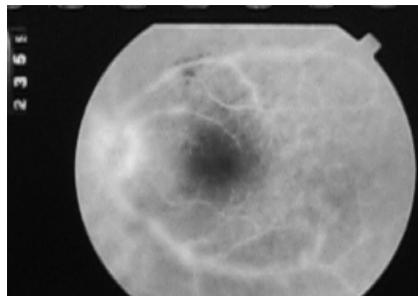
Early frame FA OD (January 1998)



Late frame FA OD (January 1998)



Early frame FA OS (January 1998)



Late frame FA (January 1998)

**Laboratory results were:**

**FTA-ABS**

*Negative*

**ACE**

*Negative*

**ANCA**

*Negative*

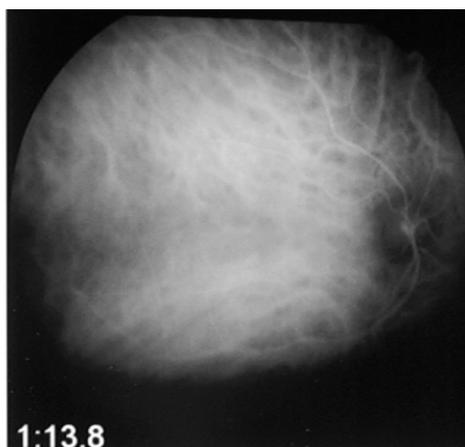
**HLA Typing**

A23, B7, **A29**, B44, Cw4 and Cw7

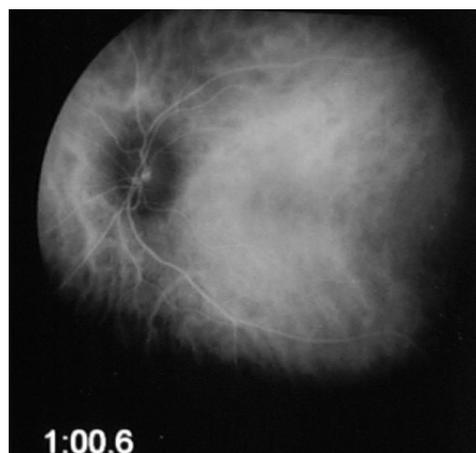
The FA was not exactly consistent with BSRC, since there was no late hyperfluorescence of the lesions that were hypofluorescent in the early frames. However, the patient was diagnosed as having BSRC due to the presence of hypopigmented lesions consistent with BSRC, vasculitis, vitritis, HLA-A29 phenotype, absence of snowbanking, and disc and vascular leakage (consistent with retinal vasculitis) apparent in the FA.

**Clinical course:**

The patient was started on cyclosporine A (CSA) 300 mg/day (=2 mg/kg). The dose of CSA was increased 2 months later to 400 mg/day, since there was a worsening in ERG findings and little improvement of vitritis. Thereafter, she was quiescent with improvement of ERG recordings; the dose of CSA was tapered to 200 mg/day over a period of 3 months. However she had a flare-up in January 1999. FA revealed no vasculitis but late staining of choroidal lesions. Indocyanine green (ICG) angiography showed hypofluorescent spots in early and late frames. The dose of CSA was increased to 400 mg/day in an effort to control active inflammation.



ICG OD (January 1999)



ICG OS (January 1999)

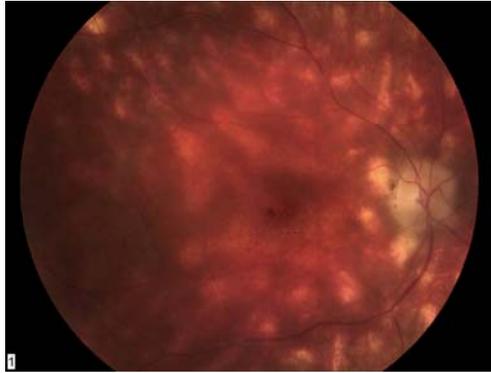
Patient was quiescent in both eyes under CSA treatment. In March 2001 CSA was tapered to 200 mg/day over a period of 4 months. There was a prominent worsening of ERG findings in December of 2001. ERG recordings during the follow-up are provided in the Table 1. Her visual acuity was 20/20 OU during this period. Mycophenolate mofetil 1000 mg/day was added to CSA (200 mg/day). She had a severe upper respiratory tract infection in February 2002 and was advised to discontinue her medications for 1 week. However, the patient did not start to take her medications and had a stomach stapling procedure and cholecystectomy in April 2002. In August 2002 there was a worsening in her ERG results. FA performed during this time revealed active vasculitis with dye leakage. CSA was resumed at a dose of 200 mg/day. In January 2004 a worsening in the ERG findings occurred, azathioprine (AZA) at a dose of 150 mg/day was added to her regimen. In April 2004 she discontinued her drugs due

to sinusitis. Patient also experienced gastrointestinal side effects while on AZA. Patient was advised to resume CSA. Since there was a worsening in ERG in February 2005 mycophenolate mofetil at a dose of 2000 mg/day was added to her regimen.

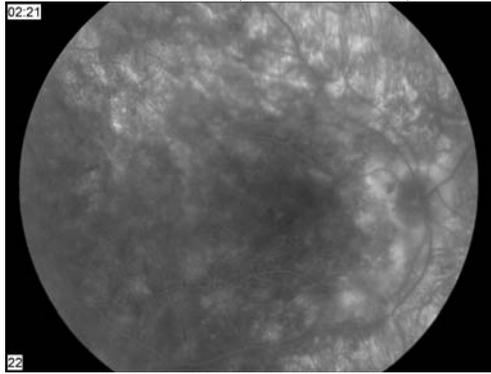
**Table 1. ERG findings over the follow-up**

<b>ERG</b>	<b>Date</b>	<b>OD</b>	<b>OS</b>	<b>Normal range</b>
<b><i>Blue (0.5 Hz) amplitude</i></b>	April 2000	<b>46</b>	<b>68</b>	100-275 $\mu$ V
"	October 2000	<b>67</b>	<b>72</b>	"
"	May 2001	<b>76</b>	<b>104</b>	"
"	December 2001	<b>49</b>	<b>58</b>	"
"	August 2002	<b>14</b>	<b>57</b>	"
"	May 2003	<b>16</b>	<b>50</b>	"
"	January 2004	<b>17</b>	<b>12</b>	"
"	July 2004	<b>&lt;10</b>	<b>31</b>	"
"	February 2005	<b>21</b>	<b>14</b>	"
<b><i>White (0.5 Hz) amplitude</i></b>	April 2000	<b>176</b>	<b>68</b>	350-700 $\mu$ V
"	October 2000	<b>270</b>	<b>279</b>	"
"	May 2001	<b>239</b>	<b>104</b>	"
"	December 2001	<b>215</b>	<b>252</b>	"
"	August 2002	<b>67</b>	<b>153</b>	"
"	May 2003	<b>112</b>	<b>250</b>	"
"	January 2004	<b>50</b>	<b>82</b>	"
"	July 2004	<b>77</b>	<b>126</b>	"
"	February 2005	<b>33</b>	<b>65</b>	"
<b><i>White (30 Hz) amplitude</i></b>	April 2000	<b>37</b>	<b>39</b>	50-125 $\mu$ V
"	October 2000	<b>40</b>	<b>46</b>	"
"	May 2001	<b>27</b>	<b>52</b>	"
"	December 2001	<b>26</b>	<b>32</b>	"
"	August 2002	<b>22</b>	<b>32</b>	"
"	May 2003	<b>26</b>	<b>46</b>	"
"	January 2004	<b>13</b>	<b>18</b>	"
"	July 2004	<b>18</b>	<b>21</b>	"
"	February 2005	<b>17</b>	<b>15</b>	"
<b><i>White (30 Hz) Implicit time</i></b>	April 2000	<b>39</b>	<b>33</b>	25-32 msec
"	October 2000	<b>36</b>	<b>32</b>	"
"	May 2001	<b>33</b>	<b>31</b>	"
"	December 2001	<b>34</b>	<b>33</b>	"
"	August 2002	<b>43</b>	<b>38</b>	"
"	May 2003	<b>42</b>	<b>40</b>	"
"	January 2004	<b>44</b>	<b>43</b>	"
"	July 2004	<b>43</b>	<b>42</b>	"
"	February 2005	<b>44</b>	<b>44</b>	"

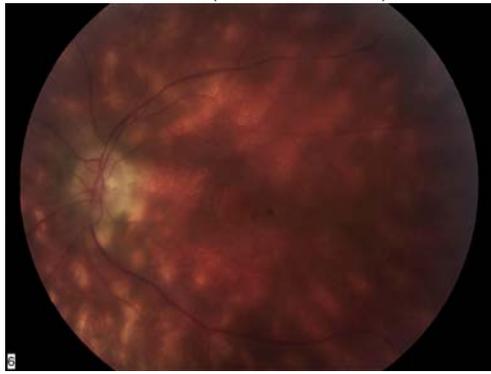
Visual acuity showed fluctuations over the follow-up period, but was never less than 20/40 for both eyes. Her last visit was in October 2005. Visual acuities were 20/40 OD and 20/25 OS. Biomicroscopy showed 1+ pigmented cells in the vitreous in both eyes. Typical birdshot lesions along with attenuated retinal vessels, RPE changes of the macula and pale optic discs in both eyes were evident on ophthalmoscopy. Fluorescein angiography showed hyperfluorescent spots due to RPE-choroid atrophy and hyperfluorescence due to RPE changes of the macula in both eyes in early and late frames.



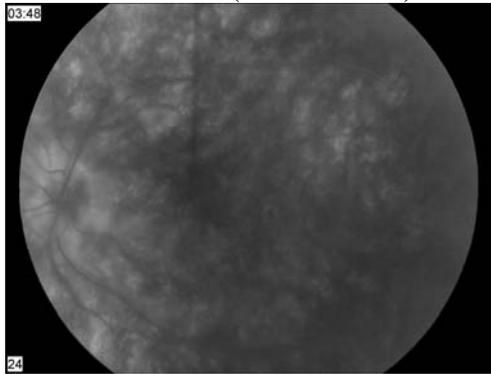
Fundus OD (October 2005)



FA OD (October 2005)



Fundus OS (October 2005)



FA (October 2005)

## **Birdshot Retinochoroidopathy**

### **Introduction**

Birdshot retinochoroidopathy (BSRC) is an inflammatory retinochoroidopathy characterized by multiple depigmented spots at the level of the retina pigment epithelium (RPE) and choriocapillaries. Fundus lesions associated with BSRC were first described by Ryan and Maumenee as “multiple, small, white spots that frequently have the pattern seen with birdshot in the scatter from a shotgun” in 1980.

### **Epidemiology**

BSRC is a rare form of uveitis. It was diagnosed in 1.2% of uveitis patients at one university referral center and was the cause of uveitis in 6 and 7.9% of patients with posterior uveitis at two institutions. The average age of onset is 50 years and the disease tends to be between ages of 35 and 70 years. Patients under the age of 30 years have been reported, but are uncommon. BSRC occurs almost exclusively among whites, with a higher incidence in persons of Northern European descent. Although some series of patients revealed an apparent gender preference for females, in two large series 54% and 58% of patients were female.

### **Clinical features**

The diagnosis of BSRC is clinical and based on the presence of a characteristic pattern of multiple depigmented retinal lesions. Patients present commonly with varying degrees of gradual, painless visual loss, frequently complaining of floaters. Both eyes are affected, although involvement may be asymmetric. Photophobia, nyctalopia and disturbances in color vision are frequently reported.

BSRC generally occurs in otherwise healthy patients. However systemic associations reported include systemic hypertension, coronary artery disease, cerebrovascular accident, vitiligo, autoimmune sensorineural hearing loss, myelodysplasia syndrome and psoriasis.

Biomicroscopic examination of the anterior segment reveals a quiet eye without conjunctival injection. There is usually minimal anterior uveitis that is nongranulomatous with fine keratic precipitates on the corneal endothelium. There is vitritis with diffuse inflammatory cells both in the anterior and posterior vitreous body. Alternative diagnosis should be considered in the absence of vitritis.

Fundus examination reveals the presence of hypopigmented lesions that are the characteristic diagnostic feature of BSRC. However, they may present years after the retinal vasculitis. They are white or cream-colored, oval or round; about 0.25-disk diameter, although when oval are often longer than 0.50-disk diameter; and they may become confluent resulting in larger geographic areas of hypopigmentation. They are usually distributed around the optic nerve head and radiate toward the periphery, more nasally and inferiorly. Biomicroscopic examination discloses that these lesions are at the level of the outer retina, RPE and inner choroid. Other clinical features include retinal vasculitis, often with cystoid macular edema (CME) and occasionally disc edema (late in the course there may be optic atrophy). The retinal vasculitis is most prominent at the posterior pole and primarily involves the veins and capillaries. Ryan and Maumenee described two additional features that they thought important to distinguish BSRC from pars planitis there are no snowballs and there are cream-colored or depigmented spots throughout the fundus. These lesions reminded the authors of birdshot, hence the name.

## **Complications**

The most common complication of BSRC is chronic cystoid macular edema (CME). Approximately half of affected eyes develop CME, and this presents a major cause of considerable visual loss from this condition. Other possible complications include epiretinal membrane formation, choroidal neovascularization, neovascularizations of the disc and/or retina, optic atrophy, cataract, glaucoma, or rhegmatogenous retinal detachment.

## **Etiology**

The etiology of BSRC remains elusive. Although the disease has been reported to occur in monozygotic twins, there is no strong familial association or an established mode of inheritance. BSRC is unique in having the strongest association between HLA and a disease. Specifically, the HLA-A29 phenotype is present in more than 95% of patients suggesting an underlying genetic predisposition for the development of the disease. The relative risk of developing BSRC in a patient with HLA-A29 phenotype has been estimated to be 50 to 224. Although there are no diagnostic tests for BSRC, the sensitivity and specificity of HLA-A29 phenotype have been estimated as 96% and 93%, respectively.

## **Pathogenesis and Pathology**

HLA-A29 has been divided into two subtypes. Previous studies using serological techniques to determine HLA-A29 subtypes in patients with BSRC were limited to evaluate the HLA-A29.1 and HLA-A29.2 subtypes. Some investigators concluded that the HLA-A29.2 subtype was more strongly associated with the risk of developing BSRC. It has also been speculated that HLA-A29.1 subtype may even be protective. A study evaluating the gene frequencies for HLA-A29 subtypes (HLA-A\*2901 through HLA-A\*2906) revealed that both HLA-A\*2901 and HLA-A\*2902 were associated with BSRC. Additional studies are required to determine whether the other, less common subtypes are associated with BSRC.

The precise role of HLA molecules in the pathogenesis of the disease is not known. The strong association between HLA-A29 and the disease suggests a primary and direct role for the HLA-A29 molecule in the pathogenesis of BSRC. The report of spontaneous uveitis with minimal anterior chamber inflammation, vitritis, retinal vasculitis, subretinal fluid with clumps of cells containing pigment, disruption of the photoreceptor cells and inflammatory cells in the choroid and optic nerve in HLA-A29 transgenic mice provides additional evidence.

The immune response in patients with BSRC is presumably to ocular self-antigens. Identifying the autoantigens involved may be useful in designing specific therapies to promote an antigen-specific tolerogenic immune response. Retinal S-antigen (S-Ag) and interphotoreceptor retinoid binding protein have been used extensively to induce experimental autoimmune uveitis in animals. Patients with BSRC were more likely to have an increase in peripheral blood lymphocytes that responded to S-Ag just before a relapse than were patients with idiopathic retinal vasculitis or Behçet's disease. Subsequently, it was also shown that peripheral blood lymphocytes from patients with BSRC also responded to bovine interphotoreceptor retinoid binding protein. There is evidence that the inflammation in BSRC starts in the inner retina, and retinal S-Ag and interphotoreceptor retinoid binding protein are located in the outer retina. The immune response to these antigens may be a secondary phenomenon caused by cellular damage (necrotic or apoptotic) with the subsequent release of previously sequestered autoantigens.

There are also studies focusing on the role of infectious agents in the pathogenesis of BSRC either directly or by inciting an autoimmune response. Association with Lyme disease and Q fever has been suggested. However, a causative role of these organisms in BSRC could not be

demonstrated. It is also possible that Lyme disease and other infections, including syphilis can mimic BSRC.

A recent report on histopathological findings of a patient's eye with BSRC that was neither blind nor phthisical contrasts with the earlier report describing the histopathology of a blind eye. This study revealed that BSRC is characterized by lymphocytic aggregations with their foci in the deep choroid, with additional foci in the optic nerve head and along the retinal vasculature. The diagnosis of BSRC in this patient was based on the characteristic fundus spots, light degree of vitreous inflammation, HLA-A29 positivity, and lack of other contributory laboratory findings. In the former report on histopathology of an eye from a patient with BSRC in 1982 focal infiltration of plasma cells and lymphocytes in the iris, ciliary body and granulomatous infiltration of the retina and choroid was described. However, the retina was more involved than the choroid, with necrosis at the junction of the retina and choroid. This eye was phthisical and had undergone previous surgery making the results difficult to interpret. This patient was also HLA-A29 negative.

### **Diagnosis**

The diagnosis of BSRC is essentially a clinical one, based on thorough ophthalmic and medical history, review of systems, and ocular examination revealing the characteristic fundus lesions associated with the disease. Laboratory work-up to exclude infectious and noninfectious causes of uveitis and ancillary testing are useful in confirming the initial clinical impression and to exclude other differential diagnostic considerations.

Ancillary testing has also been helpful in understanding the nature of subretinal birdshot lesions. The lesions are usually hypofluorescent on early and hyperfluorescent on late frames of the fluorescein angiographic studies; however, lesions noted on ophthalmoscopy may not show up on the fluorescein angiogram (FA). Indocyanine green (ICG) angiography has been shown to detect birdshot lesions more readily than FA; as such, it may be useful in determining the nature and the extent of involvement. Demonstration of lesions in ICG but not on FA provides evidence that the birdshot lesions are located in the choroid.

Two opposing theories have been proposed to explain hypofluorescent nature of the lesions observed in BSRC on ICG angiography. First is the nonperfusion of the choriocapillaries because the normal diffuse background fluorescence is not appreciated in areas of birdshot lesions. The second is the masking of the underlying hyperfluorescence from large choroidal vessels by the inflammatory lesions. It is however most probable that both of these theories play role and the hypofluorescence observed depends on the stage of the disease.

Electroretinogram (ERG) changes characteristic of this disease include a preserved a-wave, with diminished amplitude and increased latency time of b-wave, suggesting impairment of the inner retina. This represents a negative-type response, suggesting abnormal function of the neural retina with relative sparing of the photoreceptor-RPE-choroids complex. Retinal vasculopathy (determined angiographically), rather than the extent of RPE/choroidal complex involvement, has also been noted to correlate with electro-oculogram (EOG) changes. It is speculated that retinal perivascular lymphocytic infiltration seen in these patients progresses, in advanced stages, to inner retinal ischemia with the observed ERG and EOG manifestations. Investigators have also found evidence, however, for outer retinal dysfunction during the early stages of disease. Early in the course of the disease, supernormal ERG amplitudes were noted and were thought to represent retinal irritability caused by inflammation. Scotopic b-waves are usually affected before photopic b-wave, this observation and the flicker profile are consistent with rod dysfunction, especially early in the course of the disease. Given the proximity of the tissues, it may be an inflammatory response located primarily in the inner retina early in BSRC also affects outer retinal function.

The photoreceptor-RPE-choroid complex is more clearly involved later in the disease. As the disease progresses, the b-wave amplitudes progressively diminish, scotopic followed by photopic; eventually both the a- and b-waves become nonrecordable with night-blindness and clinical findings similar to those seen in retinitis pigmentosa.

Data from Dr. Foster's clinic revealed that ERG can serve as an useful adjunct in determination of initiation of tapering of immunosuppressive therapy with BSRC. In this study, 30 Hz flicker implicit times and the bright scotopic response amplitudes were shown to have most significant correlation with inability to taper medication.

### **Differential Diagnosis**

The differential diagnosis of BSRC includes the following:

<b>Inflammatory:</b>	Multiple evanescent white dot syndrome Multifocal choroiditis with panuveitis Acute posterior multifocal placoid pigment epitheliopathy Posterior scleritis Sarcoidosis Voght-Koyanagi-Harada syndrome Sympathetic ophthalmia Retinal vasculitis Idiopathic Pars planitis Secondary to systemic vasculitides
<b>Infectious:</b>	Syphilis Tuberculosis Toxoplasmosis Ocular histoplasmosis syndrome Brucellosis
<b>Masquerade syndromes:</b>	Intraocular lymphoma Metastatic carcinoma Myelodysplasia

### **Treatment**

There is a general agreement that treatment is indicated in patients with decreased vision to 20/40 or less from CME or vitritis. However, many patients with BSRC complain of such symptoms as nyctalopia, photopsia, and other visual disturbances that they often find disabling even with 20/20 Snellen visual acuity. These symptoms may also reflect abnormal retinal function that could progress and result in permanent deficits. We believe that ancillary testing is useful to guide therapy, since it is a measure of tissue dysfunction. Decline in ERG amplitude or increase in implicit time despite a good Snellen visual acuity are indicators of retinal pathology and need for immunosuppressive therapy.

Periocular or systemic steroids have not been shown to be consistently effective for BSRC, but they are still the mainstay of treatment. Although some patients may experience dramatic improvement in visual acuity in response to high doses of systemic corticosteroids or periocular triamcinolone, others may not. Systemic corticosteroids are useful in patients with severe inflammation. The vitritis, retinal vasculitis and CME are often responsive to corticosteroid therapy. However, long term treatment with systemic corticosteroids at doses 10 mg/day of prednisone (or equivalent) is not recommended. Periocular injections of depot corticosteroids are often used. But their benefits are transient, providing short-term reduction in vitreal inflammation and hastening the resolution of CME. Intravitreal triamcinolone

acetamide was reported to be effective in treating refractory CME secondary to BSRC. It has been shown to cause marked improvement in macular thickness with a corresponding dramatic increase in visual acuity that was maintained for 6 months of follow-up. With this approach, concerns arise regarding adverse events associated with the corticosteroid medication and the injection procedure.

In patients who require more prolonged therapy immunosuppressive agents are used. Fewer recurrences have been reported previously with the use of low-dose cyclosporine (2.5 to 5 mg/day) or a combination of azathioprine and cyclosporine. Intravenous immunoglobulin may be an alternative therapeutic choice. Both improvements of visual acuity and visual field as well as macular edema have been described with the use of intravenous immunoglobulin. In a recent report from Dr. Foster's clinic on the long-term follow-up of patients with BSRC treated with corticosteroid-sparing systemic immunomodulatory therapy (IMT) long term preservation of visual function has been found to be attainable. The most commonly used IMT has been cyclosporine in 92.9% of patients. Other IMT used were mycophenolate mofetil (67.9%), azathioprine (17.9%), oral methotrexate (10.7%), and daclizumab (7.1%). It has also been shown that the use of long-term immunosuppressive therapy is effective in reducing the risk of developing CME.

### **Prognosis**

The natural history of BSRC is unknown. BSRC is a chronic disease with multiple exacerbations and remissions that can extend over a period of decades. Although some investigators believe that the disease has a tendency to stabilize over a period of 3 to 4 years with remission others report on poor long-term visual prognosis. Visual loss is most commonly the result of CME and optic atrophy.

Although there are clinical reports on outcomes with corticosteroid therapy which describe a persistent worsening of vision with time, some studies focus on the treatment of the disease with corticosteroid sparing systemic immunosuppressive agents. Early institution of chronic immunosuppressive therapy has been shown to improve long-term outcomes in BSRC.

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