characterized. Two missense mutations cosegregating with alkaptonuria in 2 Spanish pedigrees and a third missense and a frameshift mutation in Slovakian families established HGO as the defective gene in alkaptonuria.12,13 Concurrently, 13 additional mutations were found in unrelated subjects with alkaptonuria from 6 European countries, Algeria, Turkey, and Japan.12,13 The latest published study7 in 1999 describes the identification of 2 homozygous missense mutations in 2 unrelated German patients who were first diagnosed with this congenital disorder after their referral to ophthalmologists. The importance of recognizing this entity, which enters in the differential diagnosis of pigmentations and deposits of the conjunctiva, is emphasized in our report, in which the recognition of this systemic disease was the initial ocular manifestation of the disease.

Patricia Chévez Barrios, MD
Ramon L. Font, MD

The authors have no relevant financial interest in this article.

This study was supported in part by grants from the Retina Research Foundation, Houston, Tex, and Research to Prevent Blindness, Inc, New York, NY. Dr Font is recipient of a Senior Investigator Award from Research to Prevent Blindness, Inc.

Arun Nayer, MD, provided the clinical photograph and additional patient history.

Correspondence: Dr Chévez Barrios, Department of Pathology, Baylor College of Medicine, One Baylor Plaza, Houston, TX 77030 (pchevez@bcm.tmc.edu).


Anterior Uveitis and Concurrent Allergic Conjunctivitis Associated With Long-term Use of Topical 0.2% Brimonidine Tartrate

Brimonidine tartrate is a relatively selective α2-agonist that lowers intraocular pressure by reducing aqueous humor production and by increasing uveoscleral aqueous humor outflow. Ocular side effects associated with brimonidine use include pruritus, as well as follicular conjunctivitis. Recently, 2 reports have described the development of anterior uveitis in 5 patients treated with brimonidine.1,2 Herein we report 4 additional cases of uveitis and concurrent allergic conjunctivitis associated with the use of 0.2% brimonidine tartrate. The 4 cases are summarized in the Table.

Report of Cases. Case 1. An 82-year-old woman sought care from her general ophthalmologist because of redness, blurred vision, and photophobia in her right eye. The patient had a history of glaucoma and had been treated with 0.2% brimonidine tartrate in the right eye during the previous 16 months. Anterior uveitis was diagnosed in the right eye and resolved after a 5-week course of topical 1% prednisolone acetate. The uveitis recurred after the corticosteroids were discontinued, and it failed to improve after 3 weeks of treatment with topical corticosteroids.

The patient was referred to a uveitis specialist, and examination disclosed conjunctival injection in the right eye with mutton-fat keratic precipitates, +2 anterior chamber cells and flare, posterior syn-

Figure 6. The large masses of ochronotic pigment (under the epithelium) and the marked actinic elastosis of the stroma stain black with the stain for elastic fibers (Movat pentachrome, original magnification ×64).
echiae, and Koepp nODULES. The left eye was quiet.

A complete blood cell count, HLA-B27 typing, fluorescent treponemal antibody absorption test, angiotensin-converting enzyme level, and chest x-ray film showed no abnormalities.

The uveitis resolved during 6 weeks of treatment with 1% prednisolone acetate, and the corticosteroids were tapered and discontinued. One month later, the uveitis recurred in the right eye and resolved with corticosteroid drops as well as discontinuation of brimonidine. After this episode of bilateral anterior uveitis, the patient experienced several flares of uveitis in the right eye presumed to be associated with her history of herpes zoster ophthalmicus, but her left eye remained quiet for 22 months.

**Case 3.** An 81-year-old woman with chronic open-angle glaucoma was examined because of photophobia and redness in both eyes of 1 week’s duration. Her ocular medications were carteolol hydrochloride and brimonidine drops for 12 months in both eyes. Examination showed mild erythema of the lids with an intense palpebral papillary reaction, conjunctival scarring, fornix shortening with symblepharon, bulbar follicles, and granulomatous keratic precipitates in both eyes. No cells were visible in the anterior chambers. Complete blood cell count, serum angiotensin-converting enzyme level, serum lysozyme level, and results of purified protein derivative test, syphilis serologic testing for syphilis, and chest x-ray film were normal.

Brimonidine was discontinued and the patient started treatment with oral prednisone and famciclovir. Four days later, the uveitis was improved and the famciclovir was discontinued. A prednisone taper was begun, and examination 2 weeks later showed no anterior chamber cells and diminished kera
tic precipitates bilaterally. After this episode of bilateral anterior uveitis, the patient experienced several flares of uveitis in the right eye presumed to be associated with her history of herpes zoster ophthalmicus, but her left eye remained quiet for 22 months.

**Summary of Cases**

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y</th>
<th>Eye(s) Affected</th>
<th>Eye(s) Treated With Brimonidine; Duration of Treatment, mo</th>
<th>Concurrent Topical Medications</th>
<th>Laboratory and Radiographic Studies†</th>
<th>Follow-up After Resolution of Uveitis, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F/82</td>
<td>OD</td>
<td>OD; 16</td>
<td>None</td>
<td>CBC, HLA-B27, FTA-ABS, ACE, CXR</td>
<td>36</td>
</tr>
<tr>
<td>2/F/83</td>
<td>OU</td>
<td>OU; 12</td>
<td>Dorzolamide hydrochloride, 0.5% timolol maleate</td>
<td>FTA-ABS, ACE, CXR</td>
<td>22</td>
</tr>
<tr>
<td>3/F/81</td>
<td>OU</td>
<td>OU; 12</td>
<td>Carteolol hydrochloride</td>
<td>CBC, FTA-ABS, ACE, lysozyme, PPD, CXR</td>
<td>18</td>
</tr>
<tr>
<td>4/M/77</td>
<td>OU</td>
<td>OU; 16</td>
<td>0.5% Loteprednol etabonate, 0.1% fluorometholone</td>
<td>CBC, FTA-ABS, ACE, CXR</td>
<td>36</td>
</tr>
</tbody>
</table>

Abbreviations: ACE, angiotensin-converting enzyme level; CBC, complete blood cell count; CXR, chest x-ray film; FTA-ABS, fluorescent treponemal antibody absorption test; PPD, purified protein derivative.

*Mean age, 81 years; mean duration of treatment, 14 months; mean follow-up, 28 months.
†Studies showed no abnormalities associated with uveitis.
logic test, and chest x-ray film were normal.

The brimonidine was stopped and the patient was treated with 1% prednisolone acetate. One week later, her conjunctivitis had resolved, the eyelids were clear, the bulbar follicles had resolved, and the keratic precipitates were reduced. The corticosteroids were tapered and the keratic precipitates resolved completely. She had no recurrences in 18 months.

Case 4. A 77-year-old man with a history of bilateral chronic open-angle glaucoma was referred to the uveitis clinic with a 6-month history of recurrent anterior uveitis and papillary conjunctivitis affecting both eyes. Ocular medications included 0.2% brimonidine tartrate for the past 16 months and 0.5% loteprednol etabonate with 0.1% fluorometholone ointment for the past several weeks in both eyes.

Bilateral papillary conjunctivitis with several mutton-fat keratic precipitates and +1 cell and flare were noted. A chest x-ray film, complete blood cell count, fluorescent treponemal antibody absorption test, and serum angiotensin-converting enzyme level were normal. The loteprednol was discontinued and 1% prednisolone acetate was begun. The uveitis was resolved during the next 4 weeks and the corticosteroids were tapered and discontinued after 10 weeks of therapy.

Twelve weeks later, the uveitis and conjunctivitis recurred. Topical corticosteroids were restarted and the brimonidine was discontinued. The conjunctivitis and uveitis resolved during the next 3 weeks. Three months later, 0.005% latanoprost was prescribed, and the uveitis had not recurred in 3 years of monitoring.

Comment. We have described 4 cases of a granulomatous anterior uveitis and concurrent conjunctivitis that appear to be related to the use of 0.2% brimonidine tartrate. All of the patients were 77 years or older and had been using 0.2% brimonidine tartrate for more than 1 year. Uveitis recurred in 1 eye rechallenged with brimonidine. In all cases, the uveitis resolved only on cessation of brimonidine treatment. Although case 2 describes recurrent uveitis in the right eye of a patient after brimonidine had been discontinued, we believe this was related to the history of herpes zoster ophthalmicus. The uveitis that occurred while the patient was using the brimonidine was distinct in its bilateral presentation and its granulomatous character.

Medication-induced uveitis has been reported with a number of drugs, including metipranolol and latanoprost, the bisphosphonates, rifabutin, cidofovir, and fomivirsen. Although such a connection was not reported in early clinical studies, brimonidine has recently been associated with the development of uveitis.1,2 The uveitis described in our report was seen with a concurrent allergic conjunctivitis. This contrasts with previous reports in which the conjunctivitis preceded the development of uveitis.1,2 As suggested by Byles et al,1 up to 15% of the patients in clinical trials developed allergic conjunctivitis and may have discontinued the brimonidine before uveitis developed.1,3

All of our patients were treated before the release of 0.15% brimonidine tartrate (Alphagan P; Allergan Inc, Irvine, Calif), which uses Purite, a preservative different from the benzalkonium chloride used in the original 0.2% brimonidine tartrate. We are unaware of reports of uveitis associated with this more recent preparation.

Overall, brimonidine is a well-tolerated topical glaucoma medication. However, the 5 cases previously reported and the 4 cases described herein suggest that 0.2% brimonidine tartrate should be considered as possible cause of drug-induced uveitis. Furthermore, clinicians considering continued use of brimonidine in the face of conjunctivitis should monitor these patients closely for signs and symptoms of uveitis.

Heidi I. Becker, MD
R. Christopher Walton, MD, MHA
Jonathan I. Diamant, MD
Michael E. Zegans, MD

The authors have no relevant financial interest in this article.

This study was supported in part by grant 1 K08 EY13977-01 from the National Eye Institute, Bethesda, Md (Dr Zegans).

Figure 2. Multiple mutton-fat keratic precipitates in the right eye (A) and left eye (B) of patient 2.
Correspondence: Dr Zegans, Department of Surgery (Ophthalmology) and Department of Microbiology and Immunology, Dartmouth Medical School, 204 Vail Bldg, Hanover, NH 03755-3842.


Optical Coherence Tomography Findings in Foveal Schisis

Juvenile retinoschisis is a congenital X-linked recessive retinal disorder. Patients may develop nystagmus, decreased central vision, or strabismus. Fundus findings vary considerably, from the absence of a foveal reflex to the presence of a large, elevated schisis cavity involving the fovea. The protean finding is a foveal schisis. Histologically, the peripheral retinoschisis is found in the nerve fiber layer. However, on review of recent literature, it is not clear where the foveal split occurs. The progression of juvenile retinoschisis is an underlying retinal pigment epithelium. Additional information may be gleaned from fluorescein angiography, electroretinography, or genetic studies.

Optical coherence tomography (OCT) is a recent advance in retinal imaging; the techniques of this modality are described elsewhere. Few case reports describe OCT imaging of this disease. We demonstrate the use of OCT to highlight unique foveal findings in a patient with juvenile retinoschisis.

Report of a Case. A 26-year-old man decreased vision and foveal schisis. This patient was previously examined and diagnosed when he was 10 years old.

The best-corrected visual acuity was 20/60 OD and 20/50 OS. Refraction was +0.50 sphere OU. Pu

![Figure 1. Red-free photographs demonstrate foveomacular schisis in both eyes.](https://archopht.jamanetwork.com/)

![Figure 2. Two-dimensional optical coherence tomographic (OCT) scan of the right eye, with horizontal (A) and vertical (B) sections through the macula. Note the broad central area of flat foveal tissue surrounded by multiple levels of schisis. Horizontal (C) and vertical (D) sections reflect similar pathologic features in the left eye.](https://archopht.jamanetwork.com/)