# Understanding and Treating
# VIRAL ANTERIOR UVEITIS

BY MARIANNE DORAN, CONTRIBUTING WRITER

*Staying on top of herpetic eye disease requires vigilance and keen powers of observation. Treatments are readily available, but vaccines, ironically, may represent a mixed blessing.*

Anterior uveitis can be puzzling and sight-threatening. But fresh insights into its viral causes may vanquish both its mystery and its danger.

Three members of the *Herpesviridae* family—herpes simplex virus (HSV), varicella zoster virus (VZV) and, most recently, cytomegalovirus (CMV)—have been cornered as causes of acute, recurrent and chronic anterior uveitis. For ophthalmologists who do not routinely encounter herpetic eye disease, the ocular manifestations of these infections can be difficult to distinguish. "The signs of herpetic eye disease can be subtle, so you need to have a high degree of suspicion," said Emmett T. Cunningham Jr., MD, PhD, MPH, who is director of the uveitis service at California Pacific Medical Center in San Francisco and adjunct clinical professor of ophthalmology at Stanford University.

"It's often very difficult to distinguish herpes simplex versus herpes zoster versus cytomegalovirus based on clinical signs alone. All three may be associated with elevated intraocular pressure, patchy or sectoral iris atrophy, and keratic precipitates that are distributed across the entire cornea," said Dr. Cunningham. Nonetheless, each viral type is paired with telltale features and epidemiologic clues that narrow the diagnosis.

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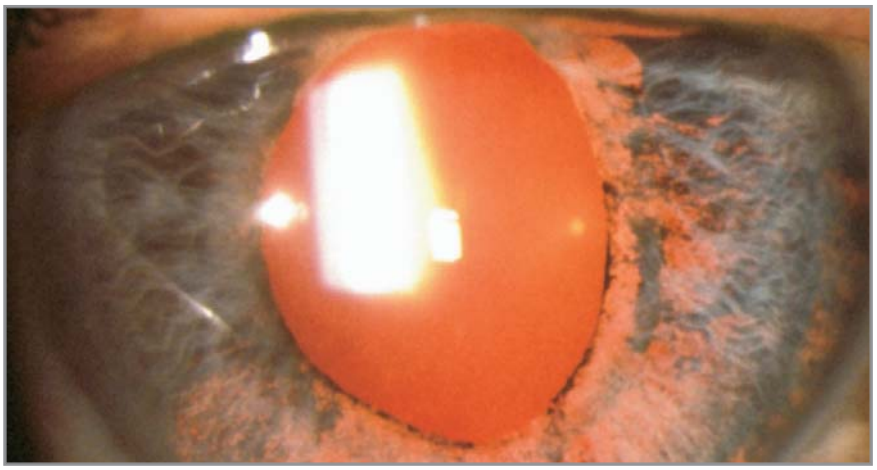

Transillumination of iris in herpetic uveitis.

## HERPES SIMPLEX VIRUS

HSV-associated anterior uveitis can occur at any age, but it tends to be more common among people under age 60. According to Dr. Cunningham, the condition is almost always unilateral, is often associated with acute ocular hypertension, and may occur with or without associated corneal involvement. Patchy or sectoral iris atrophy is quite suggestive, and a history of recurrent HSV infections on the lips or genitals can be helpful in narrowing the diagnosis, but they are not always present.

Debra A. Goldstein, MD, associate professor of ophthalmology at the University of Illinois at Chicago, noted, "HSV-related anterior uveitis is easy to diagnose if the patient has classic corneal disease. However, it can be difficult to diagnose in the absence of a history or the absence of clinical signs suggestive of herpetic keratitis."

**Signs and symptoms.** Dr. Goldstein mentioned several characteristics that can point to HSV. For example, many types of acute anterior uveitis, including those associated with the HLA-B27 phenotype, tend to alternate between eyes. A history of multiple episodes of acute iritis in one eye should alert the clinician to consider herpes, Dr. Goldstein said, even though most cases of recurrent acute iritis confined to one eye will not be herpetic. Other clinical clues that she said deserve consideration:

- Intraocular pressure. Most patients with acute iritis have low pressures. High IOP in a patient with acute iritis is suggestive of a herpetic etiology, although there are other causes of hypertensive uveitis.
- Fine stellate keratic precipitates (KPs). If KPs are diffusely distributed on the corneal endothelium, beyond Arlt's triangle, then they are suggestive but not pathognomonic of herpetic disease, Dr. Goldstein said. "Fine stellate KPs are also seen in diseases such as Fuchs' heterochromic iridocyclitis and CMV retinitis."
- Large, central, greasy KPs.
- Iris transillumination defects in a patient with iritis.
- Atrophy of the iris pigment epithelium, not just the anterior stroma.
- Presence of a dilated pupil in the absence of dilating drops.

"No single clinical feature can make the definitive diagnosis of herpetic iritis," Dr. Goldstein said, "but the presence of a constellation of these findings can help."

Dr. Goldstein and colleagues have a report now in press in the *Canadian Journal of Ophthalmology* describing these features.

**Treatment effective.** In terms of management, Dr. Cunningham said that HSV-associated anterior uveitis tends to respond well to 400 mg of oral acyclovir five times per day together with topical prednisolone acetate, 1 percent, four to eight times daily and a cycloplegic/mydriatic agent, such as tropicamide, two to four times daily. Dr. Goldstein noted that topical antivirals are not beneficial in treating herpetic uveitis, although they may be used in concert with topical corticosteroids to cover the patient in the event that herpetic epithelial keratitis develops.

Systemic antivirals—acyclovir, famciclovir or valacyclovir—are the primary treatment because they protect the cornea as well as treat the uveitis. Dr. Goldstein added that prolonged topical antiviral therapy is associated with the development of keratopathy. Extended use of topical corticosteroids also poses problems because these drugs are very difficult to discontinue in patients with herpes and require an extremely slow tapering process.

## VARICELLA ZOSTER VIRUS

VZV is well-known to family care physicians as the cause of both childhood chicken pox and, as a reactivated infection, shingles. The reactivation is often referred to as herpes zoster. Anterior uveitis related to VZV is more common among older individuals, especially those over age 60, but it can occur at any age.

"When corneal involvement is present, one suggestive feature is a unique form of pseudodendrite, which has heaped-up cells centrally, and no ulceration," Dr. Cunningham said. "This resembles a small piece of string or rope that is stuck on the cornea. Herpes zoster is also often associated with profoundly decreased corneal sensation. While it has been said that sectoral iris atrophy is pathognomonic for zoster-related eye disease, this is not necessarily true; sectoral atrophy may also be seen in the setting of HSV- or CMV-associated anterior uveitis."

Conversely, the clinical signs seen in HSV can also be present in zoster-associated uveitis, but the diagnosis is made easier by the fact that the patient almost invariably has a history of ipsilateral zoster dermatitis. Treatment for the condition is oral acyclovir, but at 800 mg five times per day—twice the

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dosage given for HSV-related anterior uveitis.

**Prevention possible.** Fortunately, physicians now have two VZV vaccines—Varivax and Zostavax, for chickenpox and shingles, respectively. Zostavax, which is recommended for people over 60 and for those with debilitating medical conditions that preclude live vaccination, reduces the incidence of shingles by more than 50 percent. Dr. Goldstein noted that the vaccine is most efficacious among people in their 60s but still has substantial efficacy among older individuals. A two-dose course of Varivax is about 70 to 90 percent effective in protecting children from chickenpox and is believed to provide immunity for about 10 years.

## CYTOMEGALOVIRUS

CMV is the pathogen most recently implicated in anterior uveitis, and it may present as acute, recurrent or chronic disease. One distinguishing characteristic may be a unique nummular KP. "Herpes simplex and zoster, we believe, are far more common causes of herpetic anterior uveitis than cytomegalovirus," Dr. Cunningham said. "For people under age 60, the vast majority of cases probably will be simplex. For those over age 60, there may be a slight preponderance of zoster, but this group still has quite a large number of simplex cases. Then there is the occasional case of cytomegalovirus. CMV should be considered in patients with signs suggestive of herpetic anterior uveitis but who fail to respond to corticosteroids and high doses of acyclovir."

Soon-Phaik Chee, MD, associate professor of ophthalmology at the Singapore National Eye Center, noted that CMV in the anterior segment is a newly described entity that occurs even in people who are not infected with the human immunodeficiency virus (HIV). It can present as acute relapsing hypertensive anterior uveitis, also known as Posner-Schlossman syndrome (PSS); Fuchs' heterochromic iridocyclitis (FHI) or corneal endotheliitis; as well as sector iris atrophy with iritis.

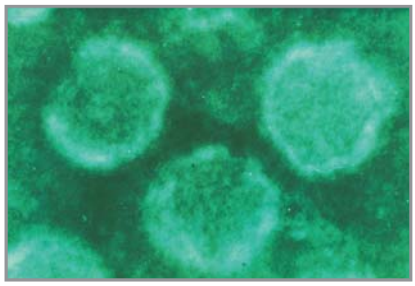
In an analysis of 15 published studies of non-HIV, CMV-associated anterior uveitis in immunocompetent patients, researchers found endotheliitis in 22 eyes of 20 patients, recurrent acute anterior uveitis and ocular hypertension in 53 eyes of 54 patients, and chronic anterior uveitis in 29 eyes of 24 patients.[1] According to Dr. Chee, eyes with CMV-associated anterior uveitis have no corneal scars, no posterior synechiae, no flare or fibrin and no posterior segment involvement.

**Posner-Schlossman syndrome.** Dr. Chee's research suggests that the median age of patients with CMV-positive PSS is 37, and about 65 percent are male.[1] The condition is unilateral, with symptoms of redness, blurring, haloes and unilateral headache. Clinical

## RUBELLA AND FUCHS' HETEROCHROMIC IRIDOCYCLITIS

Fuchs' heterochromic iridocyclitis (FHI) is having an identity crisis. It has traditionally been considered to be a syndrome characterized by a constellation of clinical findings. But in recent years researchers have recognized a more circumscribed and distinct type of FHI, one that appears to be strongly linked to the rubella virus.

"Initially Fuchs' heterochromic iridocyclitis was defined as a syndrome with the characteristic findings of heterochromia, iridocyclitis and cataract," said Dr. Cunningham. "But that definition expanded over the years to include the presence of diffusely distributed stellate KP, iris atrophy without frank heterochromia, and, in some patients, vitritis and the presence of small translucent nodules at or near the iris border. As a result, some people have suggested that a more appropriate name might be Fuchs' uveitis syndrome, or FUS." In fact, Dr. Cunningham and a colleague, Edoardo Baglivo, MD, of the Clinique d'Ophtalmologie-Hôpitaux Universitaires de Genève in Switzerland, cowrote an opinion now in press in the *American Journal of Ophthalmology* titled "Fuchs' Heterochromic Iridocyclitis—Syndrome, Disease or Both?"



Dr. Cunningham said that FUS remained an idiopathic disease until a few years ago when researchers in the Netherlands uncovered evidence implicating rubella virus in the majority of patients. Since then, others have confirmed these findings.

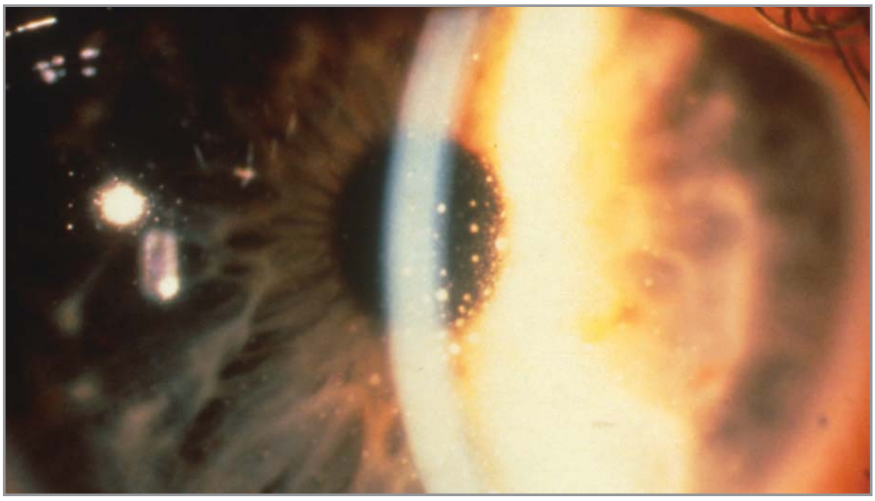
Dr. Goldstein pointed to one study in which intraocular synthesis of rubella antibodies was detected in 100 percent of patients with clinically defined FHI.[1] A second study also measured intraocular rubella antibody production and detected antibodies in 13 of 14 patients with FHI.[2] These findings received epidemiological support from a large tertiary referral center that found that the percentage of patients with FHI declined both in patients born after the introduction of the rubella vaccine in the United States and in patients born in the previous decade who were eligible to receive the vaccination.[3]

"So, on the one hand, FUS is a collection of findings that can be caused by a number of pathogens, including herpes simplex, zoster, toxoplasmosis or even recurrent sarcoidosis," Dr. Cunningham said. "But the real Fuchs'—what people are referring to when they say Fuchs' heterochromic iridocyclitis—tends to be distinctive, and the vast majority of these cases are probably related to rubella. But it is unclear whether Fuchs' is an active infection or an immune-mediated process triggered by rubella."


1 Quentin, C. D. and H. Reiber. *Am J Ophthalmol* 2004;138:46–54.

2 De Groot-Mijnes, J. D. F. et al. *Am J Ophthalmol* 2006;141:212–214.

3 Birnbaum, A. D. et al. *Am J Ophthalmol* 2007;144:424–428.



Keratic precipitates typical of Fuchs' heterochromic iridocyclitis.

features include elevated IOP, anterior chamber (AC) cells (grades ½ to 2+) and fine and medium KPs either in a ring pattern or presenting in a linear manner inferiorly. Diffuse and patchy iris stromal atrophy is common. Dr. Chee's research also suggests that about half of all presumed cases of PSS are CMV-positive and that no clinical features can differentiate between CMV-positive and CMV-negative eyes.

**Fuchs' heterochromic iridocyclitis.** According to Dr. Chee, the median age of patients with CMV-positive Fuchs' heterochromic iridocyclitis is about 65, with 80 percent of patients being male and seven percent of cases being bilateral. The main symptom is blurred vision. Clinical features include AC cells (grades 1 to 2+), fine, feathery, diffuse KPs, diffuse "moth-eaten" iris atrophy and elevated IOP.

Dr. Chee also noted that patients with CMV-positive rather than CMV-negative eyes are generally age 57 or older, male and more likely to have nodular endothelial lesions. These lesions are white, medium-sized and located in the center of the cornea. They have a translucent halo and are occasionally accompanied by a spot of brown pigment. In recent years, FHI has also been linked to rubella virus (see "Rubella and Fuchs' Heterochromic Iridocyclitis").

**Corneal endotheliitis.** Clinicians also should remain alert to the possibility of CMV-related corneal endotheliitis. "This is a diagnosis you can't afford to miss," Dr. Chee emphasized. "You should suspect it every time." In her experience, CMV endotheliitis is more common in men and among people of Chinese ancestry. The condition, which may be bilateral, typically causes blurred vision and is associated with corneal edema with Descemet's folds, as well as with fine and medium KPs that may be pigmented. Other possible clinical signs include iris atrophy, mild AC activity, reduced endothelial cell count, elevated IOP, coinlike lesions and the "owl eye sign" on confocal microscopy, representing inclusion bodies and macrophages.

Dr. Chee said it is important to confirm the diagnosis of CMV anterior uveitis with an aqueous tap, sending aqueous out for real-time PCR analysis. Most patients respond to treatment with oral ganciclovir, she added, but can relapse after the treatment is stopped.

## LONG-TERM OUTCOMES

Dr. Cunningham noted that while HSV, VZV and CMV can all be associated with recurrent disease, herpes simplex appears to be the most likely to recur, and recurrences should be treated with a five- to seven-day course of oral acyclovir at 400 mg five times per day. Herpes zoster anterior uveitis is typically acute and responds to a similarly short course of oral acyclovir, but at 800 mg five times per day.

"CMV has been treated with oral ganciclovir with good results," Dr. Cunningham noted. "But no one has reported on their long-term experiences. The drug is expensive and has some toxicity issues, so it would be dif-

## ZOSTER VACCINATIONS: Unintended Consequences?

The advent of an effective two-dose vaccine against VZV infection has no doubt spared millions of children and their families the misery of chickenpox. In theory, suppressing the virus should also reduce the incidence of herpes zoster and zoster-related eye disease as the vaccinated population ages and expands.

A potential concern, however, is that the protection offered by the varicella vaccine may not last as long, or be as robust, as the natural immunity acquired through developing chickenpox. What's more, this natural immunity is bolstered throughout an individual's life through re-exposure to children who have the disease.[1] As more young people are vaccinated—and cases of chickenpox plummet—these periodic natural immunity boosts will dwindle. The Zostavax vaccine given to prevent shingles will help compensate for this lost immunity, but it is currently given only to people over 60.

This raises questions about whether individuals born in the age of varicella vaccination will be more likely to develop herpes zoster infections in the decades to come. Moreover, will these infections develop earlier in life, be more severe or have greater potential to damage the eyes? The answers to these questions will have important implications for ophthalmologists, who may find themselves diagnosing and treating more zoster-related eye disease in the future.

1 Liesegang, T. J. *Ophthalmology* 2008;115(2)Suppl:S3–S12.

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ficult to keep a patient on it for months or years."

These infections are not without adverse effects on vision. "Herpetic anterior uveitis can have serious visual complications, including neurotrophic cornea and necrotizing retinitis. Herpes zoster typically is the most common cause of both of these conditions, but all patients with herpetic uveitis should be examined for the presence of these potentially blinding complications," Dr. Cunningham said. "Most patients who have herpetic uveitis alone do very well. If a patient has an associated keratitis, the outcome really depends upon the visual significance of any corneal scarring. When an associated retinitis is present, the prognosis is more guarded."

**Coming changes in epidemiology.** Both changes in social behaviors and the development of more vaccines will likely affect the epidemiology of herpes viral infections in the years to come. The burgeoning number of genital HSV-2 infections, for example, is expected to lead to more cases of neonatal ocular herpetic disease and to delayed cases of acute retinal necrosis syndrome.[2] Researchers also suspect that the VZV vaccine in use today may alter patterns of zoster infections over the next several decades (see "Zoster Vaccinations: Unintended Consequences?"). In addition, globalization and increased worldwide travel may deliver new viruses with sight-robbing potential to our doorstep.

For now, however, the familiar viruses require ophthalmologists' full attention. Keeping HSV, VZV and CMV in mind when examining a patient with anterior uveitis will help timely identification and treatment of these subtle but dangerous infections.


1 Chee, S. P. et al. *Am J Ophthalmol* 2008;146(6):883–889.

2 Pepose, J. S. et al. *Am J Ophthalmol* 2006;141:547–557.


## MEET THE EXPERTS


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