Infectious Uveitis

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Abstract

Infectious etiologies are implicated in many cases of pediatric uveitis. Common causes of infectious uveitis in children include toxoplasmosis, toxocariasis, and the herpes viruses. Tuberculosis is a less common cause of uveitis and is more often encountered in developing countries. Toxoplasmosis is the most common cause of posterior uveitis in children. In one recent study, 58 % of children with posterior uveitis had ocular toxoplasmosis. Infectious posterior uveitis in children can have particularly devastating visual outcomes, both because of anatomic damage and the induction of amblyopia. If an infectious etiology is suspected in uveitis, therapy should be directed against the causative organism prior to initiating steroid therapy or systemic immunosuppression.

Keywords

Uveitis • Infectious uveitis • Pediatric • Toxoplasmosis • Toxocariasis • Herpes • Cytomegalovirus • Syphilis • Histoplasmosis • Tuberculosis • Necrotizing retinitis • Rubella • Cat-scratch disease • Endogenous endophthalmitis

Abbreviations

AIDS	Acquired immunodeficiency syndrome
ARN	Acute retinal necrosis
CMV	Cytomegalovirus
CMVR	Cytomegalovirus retinitis
CNV	Choroidal neovascularization
CSD	Cat-scratch disease
DUSN	Diffuse unilateral subacute neuroretinitis
ELISA	Enzyme-linked immunoassay
FHI	Fuchs heterochromic iridocyclitis
FTA-ABS	Fluorescent treponemal antibody
HSV	Herpes simplex virus
HZO	Herpes zoster ophthalmicus
PCR	Polymerase chain reaction
PHPV	Persistent hyperplastic primary vitreous
POHS	Presumed ocular histoplasmosis syndrome
PVR	Proliferative vitreoretinopathy
RPR	Rapid plasma reagin
TP-PA	Treponema pallidum particle agglutination
VDRL	Venereal Disease Research Laboratory
VEGF	Vascular endothelial growth factor
VZV	Varicella zoster virus

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Parasitic Infections

Toxoplasmosis

Toxoplasmosis accounts for approximately 50 % of all posterior uveitis in children [1–4]. The causative organism, *Toxoplasma gondii*, is an obligate intracellular protozoan, of

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which cats are the definitive host. Humans become intermediate hosts after ingesting the cyst or bradyzoite form, which may be found in cat feces, raw meat, vegetables, or contaminated drinking water. The encysted organism then migrates to muscular or neural tissue, where it ruptures, releasing the active, or tachyzoite form [2].

Maternal-fetal transmission accounts for up to 40 % of clinical infections, the severity of which is affected by the gestational age of the fetus at the time of transmission. Fetal infection is most severe during the first trimester, and can result in hydrocephalus, intracerebral calcifications, and seizures [2, 3]. Congenital infection was previously thought to account for most cases of ocular toxoplasmosis; however, recent studies suggest that a majority of patients with ocular toxoplasmosis acquire the infection postnatally [1, 2].

Congenital toxoplasmosis typically presents with chorioretinal scars that may be detected on routine screening [2]. Macular lesions were traditionally considered to be indicative of congenital toxoplasmosis (Fig. 24.1), but it is now accepted that this finding does not reliably distinguish between congenital and postnatal infection [5]. Acquired disease may be suspected in patients with active retinitis without adjacent retinochoroidal scars [2] (Fig. 24.2). Retinal disease can reactivate after both congenital and postnatally acquired infections. Classically, these recurrences manifest as active "satellite lesions" adjacent to a preexisting retinochoroidal scar, with overlying vitritis that may be minimal (Fig. 24.3) or severe ("headlight in the fog"). Other associated findings may include disc edema, macular edema, and occlusive retinal vasculitis [5].

Ocular toxoplasmosis is typically a clinical diagnosis based on the appearance of the retinochoroidal lesion. Serologic tests may be used as supportive evidence, but are limited in utility as they can only reliably identify individuals with recent *T. gondii* infections [1, 2]. Serum anti-toxoplasma antibody titers can be detected by several serologic tests, including enzyme-linked immunoassay (ELISA), indirect fluorescent antibody test, Sabin-Feldman test, complement fixation test, and indirect hemagglutination test. Anti-toxoplasma IgM can suggest a recently acquired infection, and anti-toxoplasma IgA may also be present in active disease [2]. Anti-toxoplasma IgG presents within 1–2 weeks of infection and may persist for life, and therefore does not correlate with disease activity [6]. Analysis of intraocular fluid for antibody titers or polymerase chain reaction (PCR) to detect parasitic DNA may also assist in establishing a diagnosis of ocular toxoplasmosis [2, 7].

Toxoplasmosis is typically self-limited in immunocompetent individuals and the ocular infection usually resolves within a few months. Treatment is offered, however, in order to reduce the risks of ocular damage. Some clinicians treat only immediately vision-threatening disease in adults, but most treat all active disease in children [2, 8].

Most drugs used to treat ocular toxoplasmosis act against the tachyzoite, not the encysted, bradyzoite form of the organism. One treatment combination includes oral pyrimethamine (2 mg/kg/day for 3 days followed by 1 mg/kg/day) and sulfadiazine (25–50 mg/kg/dose four times daily). Folinic acid (10–25 mg daily) may be administered in con-

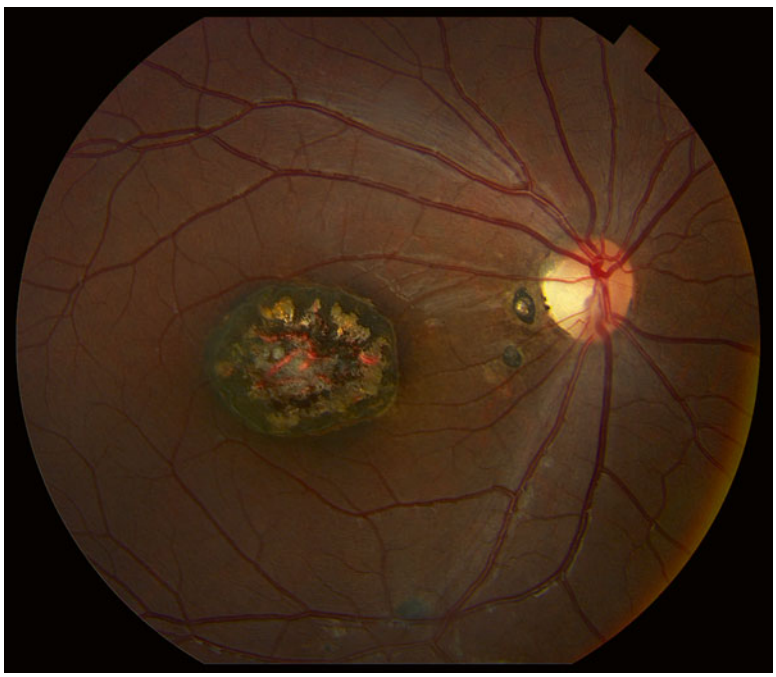

Fig. 24.1 Large chorioretinal macular scar in a case of congenital toxoplasmosis

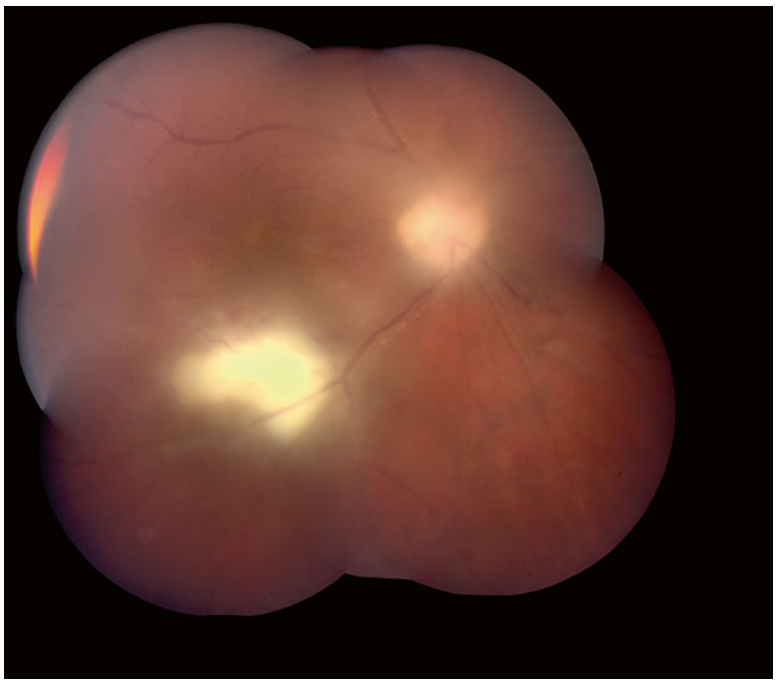

Fig. 24.2 Acquired toxoplasmosis. Note the active retinitis without an adjacent chorioretinal scar

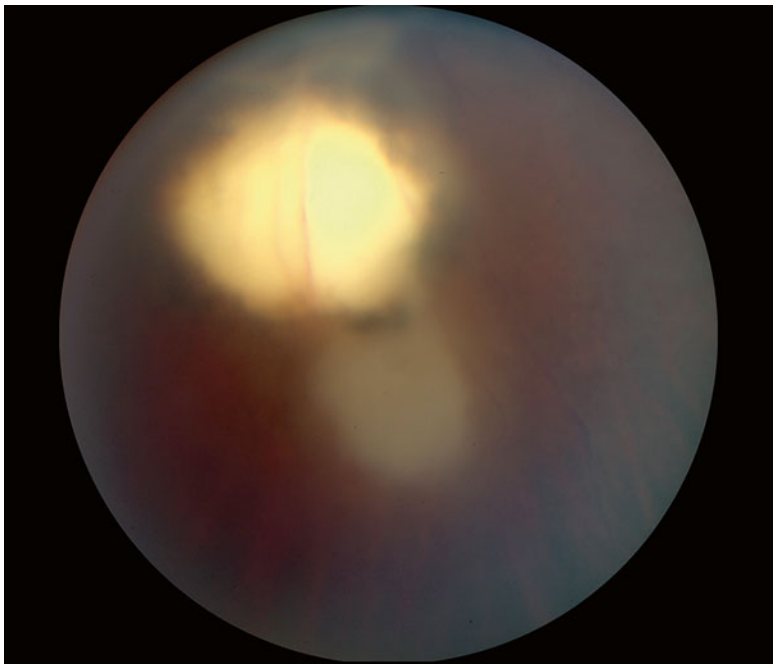

Fig. 24.3 Active inflammation adjacent to an old chorioretinal scar in a patient with reactivated toxoplasmosis

junction with pyrimethamine to prevent bone marrow suppression. Clindamycin (5–7.5 mg/kg/dose four times daily) may also be added. Newer medications such as azithromycin and atovaquone have demonstrated cysticidal effects in animal models; however this has not been demonstrated in humans and dosing recommendations for children have not been established [5, 9]. In patients with significant inflammation, oral corticosteroids may be started after initiation of antimicrobial therapy [5].

The visual prognosis depends on several factors, including the presence of macular or optic nerve involvement, and other complications of the disease such as amblyopia, macular edema, macular dragging secondary to a peripheral lesion, glaucoma, choroidal neovascularization, or retinal detachment.

Toxocariasis

Toxocariasis is a nematode infection caused by *Toxocara canis* or *Toxocara catis*, of which dogs and cats are the definitive hosts. The type and extent of clinical disease depend upon the migration pattern of the worm within the host, as well as the hosts' immune response [10].

These roundworms live in the intestinal tract of dogs or cats; humans acquire the infection after unintentional ingestion of eggs found in contaminated food or soil. The eggs then hatch into larvae in the duodenum and reach the portal circulation to cause infection [11]. Migration of the larvae into the posterior segment of the eye induces an intense inflammatory response resulting in the clinical manifestations of ocular toxocariasis.

Toxocara larvae do not develop below 50 °F, making the soil in warm climates more supportive for survival of the eggs [10, 11]. Outdoor parks are typically contaminated with *T. canis* eggs, putting children who play in these areas at higher risk of infection [11, 12]. A history of playing in sandboxes, on playgrounds, or being in contact with dogs and puppies can often be helpful in exposing risk.

Ocular toxocariasis accounts for approximately 9.4 % of all pediatric uveitis cases [13, 14]. In one study of school children, the prevalence of consultant-diagnosed toxocara eye disease was 6.6 cases per 100,000 children [15]. Ocular toxocariasis is unilateral in >90 % of cases and infection most commonly affects the pediatric population, with an age range of 2–14 years. The most common presenting signs include decrease in vision, strabismus, and leukocoria [12, 16].

Clinically, ocular toxocariasis presents in one of the three ways. Peripheral granulomas account for approximately one half of cases, and present as a white mass in the periphery [12, 16]. If there is still active inflammation, the mass may appear hazy and ill defined. As inflammation resolves, the elevated mass is typically surrounded by variable amounts of RPE pigmentary change. There may be associated retinal folds with subretinal and pre-retinal membranes extending to the macula or optic nerve (Fig. 24.4). Traction of these membranes can lead to severe vision loss and retinal detachment [10, 14]. Posterior pole granulomas are less common than peripheral ones, and present as elevated white lesions often with associated dense vitritis and tractional retinal folds. Less commonly ocular toxocariasis can present as a chronic painless endophthalmitis or dense vitritis. This presentation is more common in younger children (ages 2–9) and is often associated with the development of cyclitic membranes, retinal detachment, anterior chamber reaction, and, in severe cases, hypopyon [2, 14, 17]. Toxocariasis should be included in the differential diagnosis of conditions causing leukocoria in children, including retinoblastoma, Coats' disease, and persistent hyperplastic primary vitreous (PHPV). Shields et al. reported that 16 % of pseudoretinoblastoma eyes were actually infected with ocular toxocariasis [18].

The diagnosis of ocular toxocariasis is mainly clinical; laboratory testing thus far has proven unreliable. Serum ELISA for toxocara antibodies does not differentiate between previous exposure and current active disease, as Toxocara IgG can remain in the serum for many years [10]. In addition, the seroprevalence of toxocara antibodies is very high: 4–31 % in developed countries and up to 86 % in tropical regions [15]; thus, positive ELISA for toxocara is not diagnostic for ocular disease. In addition, false-negative test results may occur as only small amounts of antibody are released in the eye at the time of infection, with even lower serum levels [19, 20]. It is, therefore, essential that serum antibody tests are interpreted with caution, and only in the context of the clinical disease. Testing stool for ova and parasites is not useful in this disease, and unlike systemic toxocariasis, peripheral eosinophilia is not a feature of ocular

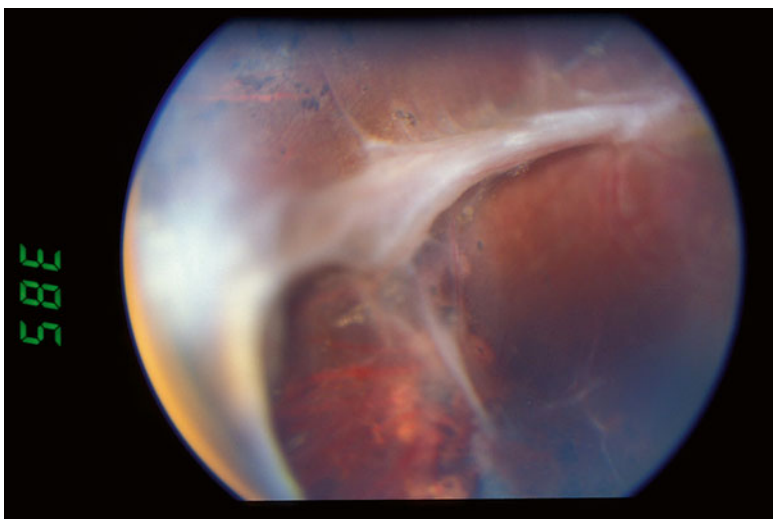

Fig. 24.4 Fundus photograph of a patient with a peripheral toxocara lesion. Note the peripheral elevated mass with adjacent RPE pigmentary change and extensive subretinal and pre-retinal membranes

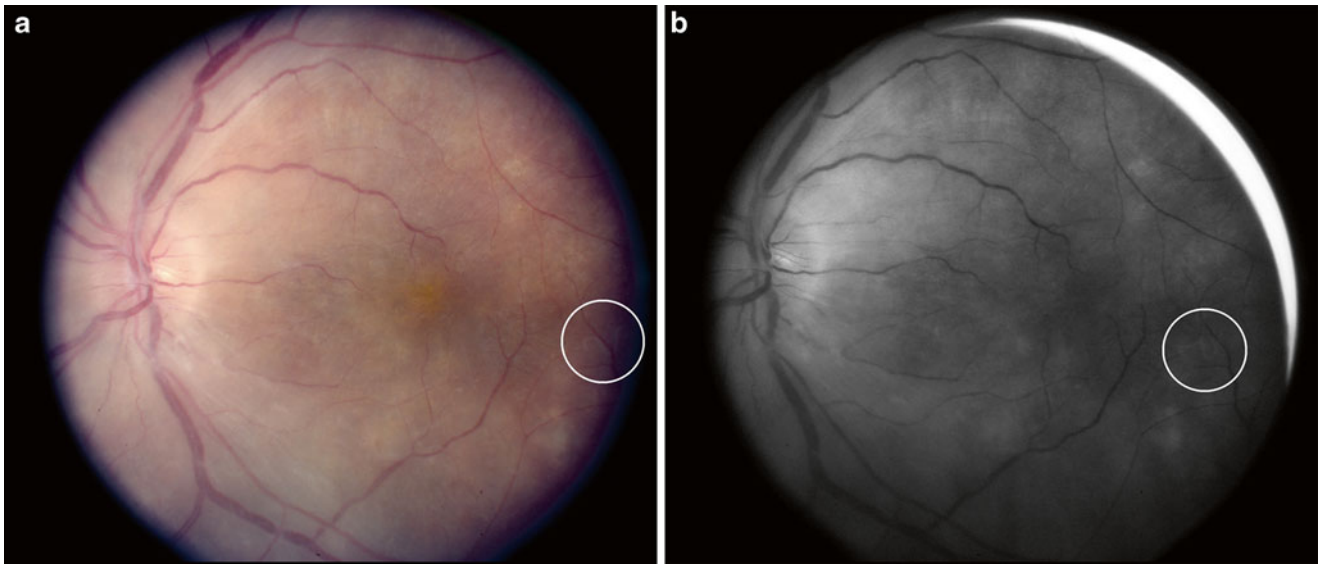

Fig. 24.5 Color fundus photograph (**a**) demonstrates subretinal worm along with vascular attenuation and diffuse RPE changes. There is also mild optic nerve edema. Red-free photo (**b**) taken minutes later demonstrates migration of the worm in the subretinal space

disease. Sampling the aqueous humor to identify toxocara antibodies can aid in the diagnosis in difficult clinical cases in which there is high clinical suspicion and negative or equivocal serum ELISA testing [19, 21]. However, this testing is not commercially available in the USA.

Treatment for ocular toxocariasis is aimed at reducing the immune response and preventing sequelae of inflammation. As the organism is presumed to be dead when the patient presents [22], the mainstay of treatment in cases with dense vitritis includes periocular or systemic corticosteroids rather than antihelminthic agents [22]. Cycloplegic agents may be added in the presence of a significant anterior chamber reaction. Surgical intervention has been successful in managing complications by relieving macular traction, repairing retinal detachments, and removing fibrotic vitreal membranes [16, 23, 24]. Visual improvement after pars plana vitrectomy was obtained in 50 % of cases in one study [23]. More importantly, prevention can be achieved through education regarding regular deworming of pets and the practicing of good hygiene.

Diffuse Unilateral Subacute Neuroretinitis

Diffuse unilateral subacute neuroretinitis (DUSN) is caused by a motile worm in the subretinal space. *Baylisascaris procyonis* and *Ancylostoma caninum* have been implicated in DUSN cases in the USA [25, 26]. *Ancylostoma caninum*, a smaller sized dog hookworm, is associated with cases described in the Southeastern USA and Latin America [25]. *Baylisascaris procyonis* is a much larger worm whose host is the raccoon and is more common in the Midwestern and Northern USA [17, 26]. Ocular infection in children occurs following ingestion of soil contaminated with larvae or eggs which hatch in the intestines and migrate via the bloodstream to the subretinal space.

DUSN most commonly affects healthy children and occurs in two clinical phases. In the acute phase, it presents as an insidious onset of unilateral decrease in vision or scotoma. The findings on examination include vitritis, papillitis, and multiple crops of gray-white lesions at the level of the retina and choroid [27]; in 40 % of cases, the live worm may be identified in the subretinal space [14, 28] (Fig. 24.5). Occasionally there may be associated vasculitis [28–30]. The retinal lesions may fade over time only to recur in another nearby location. Without treatment, worm by-products cause a local toxic effect on the retina leading to extensive retinal pigment epithelial changes [31], arteriolar attenuation, and optic atrophy. Late stages of disease are correlated with an 80 % chance of vision worse than 20/200 [32].

Electroretinographic changes occur early in the disease with evidence of damage to both cone and rod systems. The b wave is more severely reduced than the a wave, thus creating a negative ERG. Serological testing, blood smears, and stool evaluations are not helpful in diagnosing DUSN [27]. Detection of the worm in the subretinal space on dilated fundus examination is the preferred confirmatory test.

Direct application of laser photocoagulation using 200–500 μm, 0.2–0.5-s duration, can effectively destroy the nematode [14]. If the worm is located in the macula, bright light aimed directly at it may induce it to migrate, providing a much safer location to apply photocoagulation. When

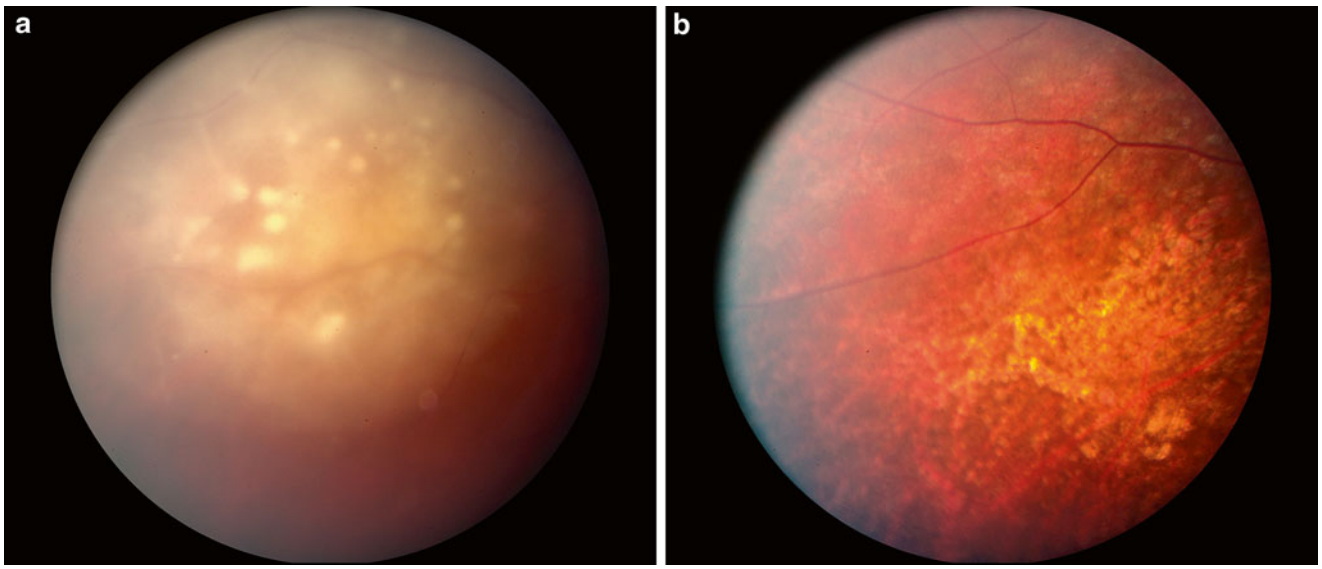

Fig. 24.6 Active syphilitic retinitis in an HIV-positive patient (**a**). Note the characteristic retinal infiltrate with superficial precipitates. Salt-and-pepper appearance of resolved retinitis (**b**) after therapy with IV penicillin

performed at an early stage in the disease course, laser treatment may improve vision and reduce inflammation [33, 34]. Once deep retinal atrophy has ensued, visual recovery is unlikely. A few studies support the use of once-daily 400 mg oral albendazole in the treatment of DUSN [30, 35]; however this has not consistently been proven, and the gold standard remains the use of laser photocoagulation [30].

DUSN should be considered in any patient with unilateral vision loss associated with vitritis, papillitis, and retinal lesions. Given the devastating visual consequences of delayed diagnosis, a careful search for the worm should be performed on every visit and, if located, treated promptly with photocoagulation.

Bacterial Infections

Syphilis

Syphilis is a systemic disease caused by the spirochete *Treponema pallidum*. It is most commonly transmitted during sexual contact, but can also occur by direct contact with infectious lesions. Congenital infection may occur transplacentally even during periods of seronegativity of the mother [2, 36].

Clinical manifestations during early congenital syphilis may include rash, hepatosplenomegaly, lymphadenopathy, and skeletal abnormalities. The most common form of uveitis in congenital syphilis is a chorioretinitis. Once inactive, it gives the fundus a "salt-and-pepper" appearance. Other ocular manifestations of congenital syphilis include anterior uveitis or interstitial keratitis, which may not present until late childhood or adolescence [2, 37]. Acquired ocular syphilis in children or adolescents presents similarly to that of adults (Fig. 24.6), and can potentially involve any ocular structure. Ocular inflammation may appear at any stage of acquired syphilitic infection and can involve the anterior or posterior segment, and may be unilateral or bilateral, and granulomatous or non-granulomatous. Because syphilis can manifest in nearly any ocular structure, it is imperative to rule out syphilis as an etiology during the work-up of any unexplained ocular inflammation [37].

Serologic tests to diagnose syphilis include non-treponemal tests and treponemal tests. Non-treponemal tests include the Venereal Disease Research Laboratory (VDRL) and rapid plasma reagin (RPR), and treponemal tests include the fluorescent treponemal antibody absorbed (FTA-ABS), *T. pallidum* particle agglutination (TP-PA), and the microhemagglutination (MHA) test. Testing for syphilis requires that both treponemal and non-treponemal tests be obtained, as non-treponemal tests may become negative over time [38, 39]. Non-treponemal tests may also produce false-positive results due to autoimmune disease, pregnancy, or infection with rickettsial or other spirochetal infections [37]. Patients with ocular syphilis should have a cerebrospinal fluid examination and be referred to an infectious disease specialist. Intraocular syphilis should be treated as neurosyphilis, regardless of the results of lumbar puncture [40]. Treatment of neurosyphilis in adults includes intravenous aqueous penicillin G 18–24 mU/day for 14 days, or procaine penicillin G 2.4 mU/day intramuscularly plus probenecid 500 mg intramuscularly four times a day for 10–14 days. Children with

congenital syphilis or neurologic involvement should be treated with intravenous aqueous penicillin G 200,000–300,000 units/kg/day, administered as 50,000 units/kg every 4–6 h for 10 days [41]. Any patient diagnosed with syphilis should also have HIV testing, as studies have demonstrated that up to 83 % of patients with posterior manifestations of ocular syphilis are coinfected with HIV [38].

Cat-Scratch Disease

Cat-scratch disease (CSD) is caused by the facultative intracellular gram-negative rod *Bartonella henselae*. It typically occurs in immunocompetent patients under 20 years old, and is more common in males [42]. Transmission occurs through the bite or scratch of an infected cat. Systemic manifestations include a mild-to-moderate influenza-like illness with painful lymphadenopathy [42]. The eye is commonly affected, and clinical manifestations may vary.

The most common ocular complication of CSD is Parinaud oculoglandular syndrome, which presents with a follicular conjunctivitis and is associated with regional lymphadenopathy and fever. On examination, there is unilateral conjunctival injection, epiphora, and discharge. Conjunctival lesions may be present on the palpebral or bulbar surfaces and ulceration with necrosis of the epithelium is common. Other organisms reported to cause Parinaud oculoglandular syndrome include tuberculosis, syphilis, and sporotrichosis [42, 43].

Other ocular manifestations of CSD include neuroretinitis, retinitis and choroiditis, retinal infiltrates, retinal vasculitis and vascular occlusions, and disc edema [42–44]. Neuroretinitis with macular star formation has classically been considered the most common intraocular finding associated with CSD; however recent reports suggest that isolated lesions in the outer retina and choroid may be more common than previously reported [42, 44, 45].

Diagnosis of CSD is based on clinical findings that can be supplemented with laboratory tests. Serologic tests include indirect fluorescence assay and ELISA. Polymerase chain reaction may also be useful; however its sensitivity is lower than that of serological tests [42].

In immunocompetent patients, CSD is often a self-limiting disease, and therefore treatment may be reserved for those with severe infections or for immunocompromised patients. However, there are reports that demonstrate a benefit to antibiotic therapy in those with CSD retinitis. Doxycycline (100 mg orally twice daily) combined with rifampin (300 mg orally twice daily) has been used successfully. Doxycycline should be avoided in patients younger than 12 years of age due to the risk of tooth discoloration [42].

Lyme Disease

Lyme disease is a multisystem infection caused by the spirochete *Borrelia burgdorferi*, which is transmitted to humans by the *Ixodes* tick [2, 46]. The preferred host for the adult tick in the USA is the white-tailed deer [46]. Most cases of Lyme disease in the USA occur in the Mid-Atlantic and Northeastern regions.

Lyme infection is described by its three distinct stages. Stage 1 involves the classic target lesion of erythema migrans, flulike symptoms, and lymphadenopathy. Transient mild bilateral conjunctivitis and episcleritis can be seen in early disease [46]. Stage 2 infection occurs days to weeks later and is characterized by cardiac and neurological involvement. Bell's palsy may occur during this stage [47]. The third stage manifests with chronic fatigue, painful episodes of arthritis, and neurological symptoms such as ataxia, encephalomyelitis, and dementia [46]. Ocular manifestations of Lyme disease generally occur in the later stages and can include optic neuritis, cranial nerve palsies, interstitial keratitis, and uveitis [48]. Most commonly, uveitis presents as a bilateral intermediate uveitis associated with granulomatous iridocyclitis, typically associated with peripheral snowbanking and exudates [46, 47]. Posterior uveitis has also been reported in the form of a diffuse choroiditis with cystoid macular edema and exudative retinal detachment [49]. Retinal vasculitis has also been reported [48, 50]. Bilateral keratitis occurs in approximately 4 % of children with chronic Lyme arthritis [51].

Diagnosis of Lyme disease can be challenging as *B. burgdorferi* is extremely difficult to culture. A clinical history describing a tick bite in an endemic area followed by characteristic rash is suggestive of infection; however, most patients do not recall being bitten by a tick. A fourfold increase in serial IgM antibody levels in a patient with a clinical history consistent with Lyme disease increases the probability that Borrelia infection is the cause of symptoms [52]. In the acute phase, most patients have not yet mounted a sufficient antibody response and tests will be falsely negative [52, 53]. The sensitivity of an ELISA done at least 5 weeks after disease onset approaches 90 %; however positive results must be confirmed with Western blot [52]. False-positive ELISA results are common, and can occur with autoimmune disease and Rocky Mountain spotted fever, or as a result of immunologic cross-reactivity with treponemal antibodies in cases of syphilis or relapsing fever [53–55].

Severe posterior uveitis associated with Lyme infection should be treated with IV antibiotics such as ceftriaxone (100 mg/kg/day IV × 21 days) or penicillin G (250,000 units/kg/day IV daily × 21 days). Topical corticosteroids and mydriatics can be used for anterior segment inflammation [47]. Mild ocular disease not involving the posterior segment can

be treated with oral antibiotics such as doxycycline or amoxicillin.

Lyme infection is a rare cause of uveitis. More commonly patients will experience mild conjunctivitis or cranial nerve palsies. Clinical diagnosis depends on a suggestive history followed by elimination of other more likely causes. Serum testing is not diagnostic and should be interpreted with caution. Confirmed cases of uveitis should be treated with appropriate intravenous antibiotics.

Intraocular Tuberculosis

Nearly one-third of the world's inhabitants are infected with *Mycobacterium tuberculosis* but only 10 % of those will develop active disease. Worldwide tuberculosis prevalence among children was estimated at 530,000 cases in 2012, approximately 6 % of the 8.6 million cases worldwide [56]. Tuberculosis (TB) is characterized by multiple foci of granulomatous inflammation most commonly affecting the lungs, although it may spread to any solid organ [57]. Ocular involvement was found in 1.39 % of 1005 cases of pulmonary and extrapulmonary TB in a study from India [58]. Most patients with tuberculous uveitis however present without concurrent systemic disease [59–61]. Ocular TB carries risks of significant visual morbidity and is associated with a 30 % enucleation rate [62].

In patients in endemic areas, the ocular signs most predictive of tuberculous uveitis include broad-based posterior synechiae, retinal vasculitis with or without choroiditis, and serpiginous-like choroiditis [63]. In nonendemic areas, posterior uveitis with multiple choroidal granulomas is the most common clinical presentation of intraocular tuberculosis, followed by anterior uveitis and panuveitis, although retinal vasculitis and neuroretinitis, scleritis, and serpiginous-like choroiditis are also described [57, 61, 64, 65].

Tuberculous choroidal granulomas are grayish white to yellow nodules with indistinct borders, occasionally associated with overlying serous retinal detachment [66]. As the infection resolves, the margins become more distinct with a pigmented border resulting in an atrophic scar [67]. Liquefaction necrosis can occur as the bacilli multiply and caseation becomes present within the granuloma, leading to the development of subretinal abscesses [68]. Plaque-like choroidal lesions displaying an advancing border represent the serpiginous-like choroiditis associated with tuberculous uveitis [69]. Less commonly, a large solid tuberculoma may mimic a choroidal tumor [70].

Retinal vasculitis typically presents as an obliterative periphlebitis with retinal hemorrhages and areas of nonperfusion [64, 65]. Anterior uveitis is generally granulomatous, with mutton fat keratic precipitates, iris nodules, and, rarely, tuberculous granulomas in the anterior chamber angle [63].

Diagnosis of intraocular tuberculosis is complicated by the challenge of ocular sampling for microbiological confirmation of disease. Recommended diagnostic criteria for presumed ocular tuberculosis include clinical findings consistent with intraocular TB infection, as well as positive testing such as tuberculin skin testing, interferon gamma release assay, radiologic findings, or cultures from extrapulmonary sites of infection, a positive response to a therapeutic trial of four anti-tuberculin medications, as well as exclusion of other causes of intraocular inflammation [61, 67]. Additional tests to confirm the diagnosis include identification of the organism in ocular fluid either by culture or PCR; however the yield is very low and testing carries the risk of morbidity [71, 72]. Cultures of *M. tuberculosis* on Lowenstein-Jensen media can take as long as 8 weeks [67] and the sensitivity of polymerase chain reaction in vitreous samples is less than 50 % [71].

The recommended treatment for ocular tuberculosis involves the use of various combinations of specific antituberculous medications including isoniazid, rifampin, ethambutol, and pyrazinamide. Therapy should include a multidrug regimen continued for at least 8–9 months [57, 60, 73]; ocular disease may require longer therapy than is required for pulmonary disease [61]. These medications carry risks of systemic toxicity; thus management should be done in conjunction with a pediatric infectious disease specialist. Sequestered organisms have been identified in the retinal pigment epithelium of enucleated specimens and are likely responsible for disease reactivation [74]; thus relapses of posterior segment disease should also be treated with specific anti-mycobacterial therapy.

Ocular tuberculosis may be associated with significant morbidity. In cases without systemic evidence of disease or microbiological confirmation of infection, a high index of suspicion is required to make the diagnosis and prevent delay in treatment.

Viral Infections

Herpes Simplex Keratouveitis

Herpes simplex is a ubiquitous DNA virus responsible for the pathogenesis of many ocular infections. Herpes simplex virus (HSV) type 1 is most commonly acquired during childhood via contact with infected saliva or mucous membranes, while type 2 can be acquired by exposure to active lesions during vaginal delivery or through transplacental spread [75]. The virus then becomes latent in the corresponding sensory ganglia where it may reactivate later [76]. Ophthalmic infection is generally a manifestation of virus reactivation in the trigeminal ganglion.

HSV uveitis is a challenging disease to manage in children due to the added risk of amblyopia secondary to corneal scarring and astigmatism in patients with associated corneal involvement. Herpes simplex keratitis and uveitis are typically unilateral in adults, with the exception of individuals with atopic disease, but may present bilaterally in children [77].

The diagnosis of herpes simplex keratouveitis is easily made in a patient with a typical dendritic epithelial lesion. However, making the diagnosis of herpes simplex iridocyclitis without evidence of keratitis can be more challenging. A careful history should include a search for exposures, coexisting atopic or dermatologic disease, recent vaccination, and a history of prior herpetic disease [78]. Examination may reveal inflammatory cells in both the anterior chamber and anterior vitreous owing to iris and ciliary body inflammation. The uveitis is often granulomatous with pigmented keratic precipitates not confined to the inferior cornea and iris nodules, and may be associated with a hypopyon or hyphema [78–81]. Iris transillumination defects are common due to ischemic atrophy of the iris pigment epithelium [78, 80, 82] (Fig. 24.7). Distortion of the pupil may occur due to a combination of localized sphincter damage and the presence of posterior synechiae [78, 79, 82], and the pupil is often larger in the involved eye [83]. The condition is commonly associated with elevated intraocular pressure at presentation [78, 82], helping to differentiate it from other causes of acute anterior uveitis, where ciliary body inflammation typically results in a reduction in IOP. The disease may run a chronic or recurrent course, and prophylactic treatment may be indicated. Confirmation of diagnosis can be made by PCR detection of viral DNA in aqueous humor samples [84].

The recommended treatment for herpes simplex keratouveitis in children involves the use of systemic antiviral medications. Oral acyclovir is dosed from 12 to 40 mg/kg/day in divided doses depending on the renal health of the child and disease severity [85]. Oral valacyclovir has higher bioavailability with less frequent dosing, is well tolerated, and has been shown to be effective in children. Dosing recommendations in the pediatric population have not yet been established; however adult dosing (1 g twice daily) can be given to older children [86]. Early trials with famciclovir demonstrated favorable results in children aged 1–12 years, but further studies are warranted and no pediatric formulation is available [87]. Cycloplegics may be added to improve comfort and prevent development of posterior synechiae, and topical antihypertensive agents may be required o control intraocular pressure. If there are no corneal epithelial defects, topical corticosteroids can be added [88]. The addition of topical steroids in herpetic disease should only be used with simultaneous topical or systemic antiviral coverage. Prolonged antiviral treatment can be used to reduce recurrences.

Varicella Zoster and Herpes Zoster Ophthalmicus

The varicella zoster virus (VZV) belongs to the family of herpes viruses and is responsible for two distinct clinical entities: varicella (chickenpox) and herpes zoster (shingles). Since the introduction of the childhood VZV vaccine, many children no longer experience wild-type chickenpox infection and varicella-related morbidity has declined dramatically [89].

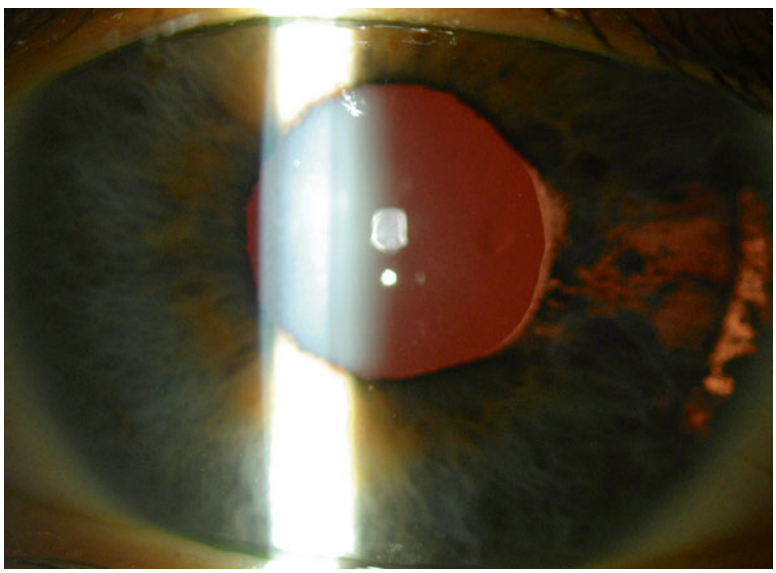

Fig. 24.7 Slit-lamp photograph demonstrating sectoral iris transillumination defect in a patient with HSV anterior uveitis

Intraocular inflammation may occur in the setting of systemic varicella infection or as part of VZV reactivation during an episode of shingles. Ocular manifestations of systemic varicella infection are less common than those that occur during zoster reactivation and may include eyelid lesions, conjunctivitis, disciform keratouveitis, and anterior uveitis [90–93]. Approximately 12–25 % of children with active chickenpox lesions develop a mild anterior uveitis [90]. Ocular involvement does not correlate with the presence of eyelid lesions or the severity of the chickenpox infection [93].

Herpes zoster reactivation (shingles) is more frequent with advancing age or immunosuppression. However, childhood cases have been reported. Risk factors for herpes zoster in children younger than 10 years of age include varicella acquired in the first year of life or VZV exposure in utero from maternal gestational infection [94]. In children older than ten, infection typically occurs in the setting of immunosuppressive medications, human immunodeficiency virus infection, or malignancy [94, 95]. Ocular involvement during herpes zoster infection occurs in 60–71 % of cases involving the ophthalmic division of the trigeminal nerve [96]. Hutchinson's sign describes involvement of the nasociliary branch, with skin lesions developing on the tip of the nose, and is a strong predictor of intraocular inflammation and poorer visual outcome [97].

Herpes zoster ophthalmicus (HZO) can involve any portion of the eye causing blepharoconjunctivitis, episcleritis, scleritis, sclerokeratitis, uveitis, retinal necrosis, optic neuritis, or oculomotor palsies, and is typically more severe than ocular disease that occurs during primary varicella infection [95, 96].

Uveitis occurs in 30–50 % of cases of HZO, and often presents 1–2 weeks after the onset of skin or corneal lesions, but can also manifest without evidence of prior or concurrent epithelial or stromal disease [82]. Anterior uveitis is similar to that observed in herpes simplex infection, and examination may demonstrate keratic precipitates, synechiae, pupil distortion from sphincter atrophy, and iris transillumination defects [96]. Hyphema has also been reported as a complication of herpes zoster uveitis [98], and intraocular pressure is often elevated. Since necrotizing retinitis may develop, every patient with HZO requires a dilated fundus examination. Diagnosis can be made based on the medical history and the presence of the typical dermatomal rash; however a small number of patients demonstrate zoster sine herpete and have only ocular disease with no skin lesions [99]. In difficult cases, viral culture from corneal scrapings or aqueous PCR can be helpful [100].

Ocular involvement in primary varicella can be self-limited or may require a short course of cycloplegic and topical steroids. Most cases heal without complications and the prognosis is good [90]. Conversely, herpes zoster ophthalmicus is much more difficult to treat and the course may be prolonged. Treatment of HZO involves use of oral antivirals such as acyclovir, valacyclovir, and famciclovir. For children weighing less than 40 mg, oral acyclovir can be given as 20 mg/kg/dose four times daily. For children weighing over 40 kg, 800 mg four times daily is effective. Pediatric dosing for oral valacyclovir and famciclovir has not yet been elucidated [9]. Topical corticosteroids are used for isolated stromal or nummular keratitis and for anterior uveitis. Anterior uveitis often persists for weeks or months and may respond to topical corticosteroids, cycloplegics, and topical antihypertensives, although systemic antiviral therapy is usually required. Long-term therapy often is needed due to residual damage caused by the inflammatory reaction. Surgical management may be required for lid abnormalities, corneal scarring, glaucoma, or cataract development [96]. Persistent corneal hypoesthesia has been found in 90 % of children with HZO and is a long-term risk factor for neurotrophic complications [101].

Necrotizing Retinitis

Acute retinal necrosis (ARN) was first described in 1971 by Urayama and associates as a severe vaso-occlusive retinal necrosis [102]. Histopathological identification of the herpes virus in the retina of patients with ARN was made in 1982, paving the way for directed therapy [103]. Acute necrotizing herpetic retinitis is an uncommon cause of pediatric uveitis; thus keeping a high clinical index of suspicion is crucial to diagnosis.

In contrast to ARN in adults, where varicella zoster is the most common etiology [104], ARN in the younger population is more frequently associated with reactivation of herpes simplex type 2 [105, 106]. Retinal necrosis has been reported following congenital HSV 2 encephalitis and meningitis; however in most cases no previous neonatal infection exists, and perinatal contact with maternal lesions is thought to be the source [107].

Acute retinal necrosis in children may be accompanied by fever in addition to the typical symptoms of blurred vision, photophobia, floaters, and pain [106, 107]. The fellow eye may become affected in 36 % of patients, weeks to months later [108]. Granulomatous anterior uveitis often accompanies posterior disease, and therefore examination of the peripheral retina is essential to avoid misdiagnosis.

The diagnostic criteria for ARN established by the Executive Committee of the American Uveitis Society include (1) one or more foci of retinal necrosis with discrete borders in the peripheral retina (Fig. 24.8), (2) occlusive arteriolar vasculopathy, (3) circumferential spread, (4) vitreous and anterior chamber inflammatory reactions, and (5) rapid progression of disease without treatment. An important characteristic that differentiates this condition from other

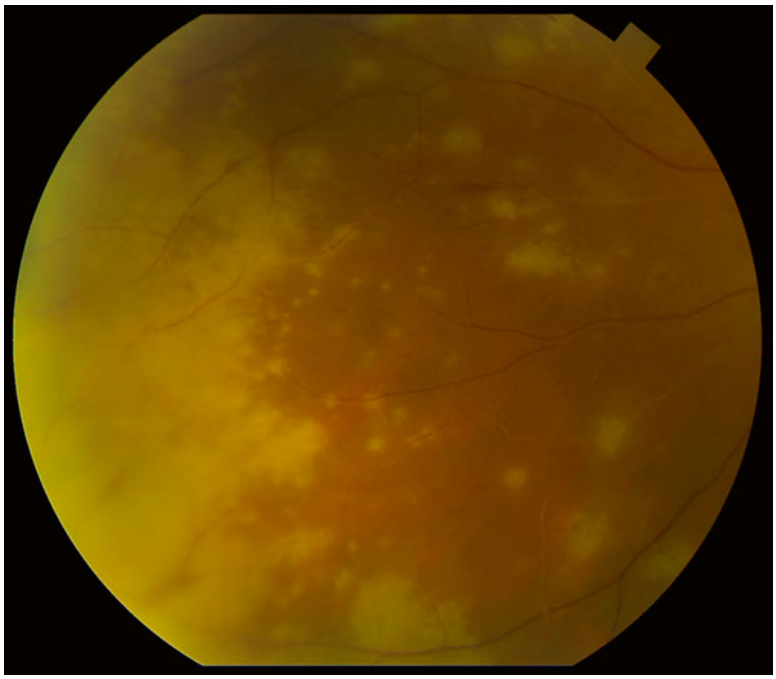

Fig. 24.8 Peripheral areas of confluent retinal whitening with occlusive vasculitis in acute retinal necrosis

entities is that the lesions do not follow the retinal vascular architecture [109].

Acute retinal necrosis must be considered in any patient who presents with peripheral retinitis and retinal vasculitis; a prompt diagnosis is necessary given the rapid progression of disease and risk of permanent vision loss. Clinical diagnosis may be supported with confirmation of viral etiology by PCR. PCR of aqueous or vitreous specimens is highly sensitive and can confirm clinical suspicion as well as determine the responsible virus [110].

Prompt treatment with systemic antiviral medication is essential to hasten resolution in the affected eye and prevent contralateral infection. Presently, there is no single standard of care for ARN, and many options for antiviral treatment exist. A common strategy is to initiate therapy with intravenous acyclovir or valacyclovir for 10–14 days, followed by extended therapy with oral acyclovir [9, 108, 111]. For children able to take adult dosing, sole therapy with oral valacyclovir (1–2 g three times daily) or famciclovir (500 mg three times daily) can be given due to their greater bioavailability and intraocular penetration [9, 112, 113]. Adjunctive therapy should be considered for foveal threatening disease, and includes the use of intravitreal antivirals such as ganciclovir (2 mg/0.05 ml) and foscarnet (1.2 mg/0.05 ml) [9, 111, 114]. Meghpara et al. showed that in patients with moderate retinal involvement in ARN (25–50 % retinal involved) intravitreal therapy can stabilize or improve visual acuity [115]. In pediatric cases of ARN that are resistant to acyclovir, intravenous foscarnet (40–60 mg/kg/dose every 8 h) has been shown to be beneficial; however precise dosing calculations should be made by a pediatric infectious disease specialist [116]. Systemic corticosteroids may be added after antiviral therapy is initiated, in order to decrease reactive inflammatory tissue damage; dosing should be adjusted based upon clinical severity.

The predominant complication of ARN is rhegmatogenous retinal detachment, occurring in 60 % of pediatric cases in one series [107]. Thus, a thorough peripheral examination in search for retinal holes should be performed at every visit. Prophylactic laser barricade has been shown in some studies to reduce the risk of retinal detachment, although this recommendation has not been consistently supported [111, 117–119]. Surgical repair retinal detachment may be complicated by the posterior location of breaks, presence of multiple large holes in necrotic retina, and proliferative vitreoretinopathy (PVR). Repair often requires vitrectomy with silicone oil and/or scleral buckle [108]. Despite aggressive management, the development of epiretinal membranes, optic atrophy, macular scarring, and PVR may limit final visual acuity [107].

Cytomegalovirus

Cytomegalovirus (CMV), a member of the herpes virus group, is the most common congenital viral infection in the USA [120], and can result in intrauterine growth retardation, microcephaly, hepatosplenomegaly, hearing impairment, and mental retardation [121, 122]. Ophthalmologic abnormalities are common in CMV infection and include visual impairment from optic atrophy or cortical visual impairment, macular scars, and chorioretinitis [120, 123]. CMV retinitis

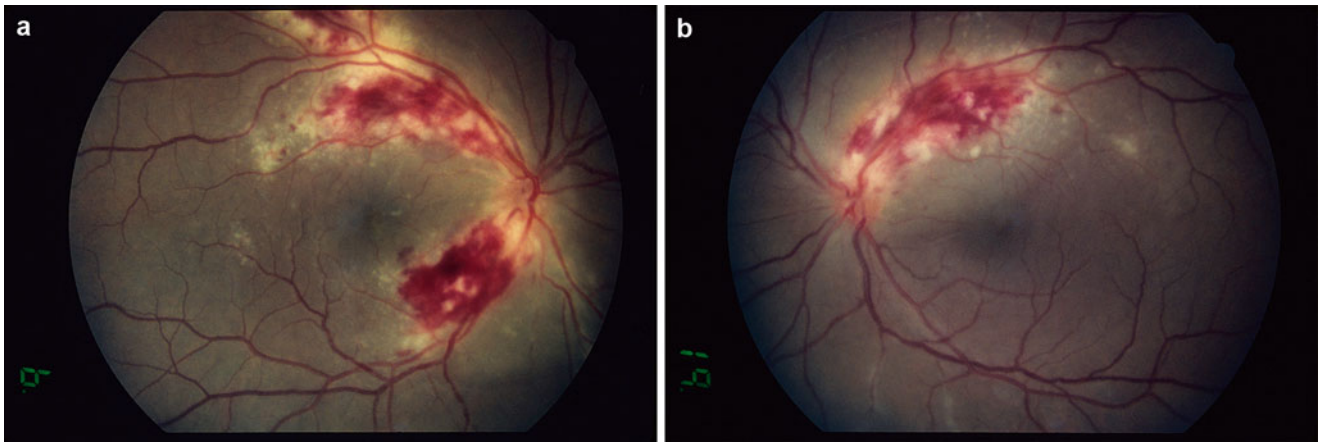

Fig. 24.9 (**a** and **b**) Bilateral cytomegalovirus (CMV) retinitis in an immunosuppressed patient demonstrating retinal necrosis and hemorrhages along the distribution of retinal vessels in the posterior pole

(CMVR) has been reported in up to 25 % of symptomatic congenital CMV patients [122, 124].

CMV is a common viral cause of retinitis in immunocompromised individuals, such as those with acquired immunodeficiency syndrome (AIDS) or in those who are iatrogenically immunosuppressed after solid organ transplantation [2]. Between 20 and 40 % of adults with AIDS may be affected with CMVR, while it has only been reported in approximately 5 % of children with AIDS [125–127]. Similarly, it is rare in children with other systemic etiologies of immunosuppression, although it has been reported in patients with severe combined immunodeficiency syndrome and renal or bone marrow transplantation, and those undergoing chemotherapy for acute lymphocytic leukemia [126, 128].

CMV retinitis may begin as retinal whitening and necrosis along retinal blood vessels, often with associated hemorrhage (Fig. 24.9). Multifocal, granular lesions and vasculitis may also occur. Full-thickness necrosis can result in retinal thinning, multiple large retinal holes, and retinal detachment [2].

The clinical presentation of CMVR in children differs from that of adults. Young children may be unable to describe visual changes, such that retinitis is detected only during screening examination performed because of extraocular CMV or HIV infection. This delay in diagnosis may contribute to the higher proportion of bilateral, macula-involving retinitis at initial presentation in children, and subsequent poor visual outcome. Baumal et al. found that CMVR was bilateral in 89 % of immunocompromised children at diagnosis, whereas only approximately one-third of adults with AIDS have bilateral CMVR at initial presentation [126, 129].

CMV retinitis is typically a clinical diagnosis; however PCR of anterior chamber or vitreous fluid may be helpful. Treatment induction can be achieved with intravenous ganciclovir (5 mg/kg every 12 h), intravenous foscarnet (60 mg/kg every 8 h), or oral valganciclovir. Dosing of valganciclovir in pediatric patients has not yet been agreed upon [9, 126]. Induction therapy is generally continued for 2–3 weeks. Decisions regarding dosing maintenance or suppressive therapy should be made in conjunction with a pediatric infectious disease specialist. Intravitreal ganciclovir (2 mg/0.05 ml) and foscarnet (1.2 mg/0.05 ml) may also be used as adjunctive therapy in children with retinitis who have failed to completely respond to or do not tolerate systemic therapy [9, 126, 130, 131].

Rubella

Congenital Rubella syndrome is classically characterized by a combination of cardiac, ocular, and hearing defects. The rate of in utero transmission and severity of fetal infection is largely correlated with gestational age at the time of maternal infection. Ocular disease may occur in up to 78 % of children. Typical findings include pigmentary retinopathy, cataracts, microphthalmia, and glaucoma [132].

In addition, the rubella virus has been implicated in the etiology of Fuchs heterochromic iridocyclitis (FHI) [133–136]. Typical findings in FHI include iris heterochromia, unilateral anterior uveitis with stellate keratic precipitates, anterior stromal iris atrophy, and the development of posterior subcapsular cataract [137]. Antibodies to the rubella virus have been detected in the aqueous humor of patients diagnosed with FHI and may represent chronic infection [133, 135, 138]. FHI has become less common in the USA with the introduction of rubella vaccination [136].

Fungal Infections

Histoplasmosis

Presumed ocular histoplasmosis syndrome (POHS) is a distinct ocular syndrome that develops following systemic infection with *Histoplasma capsulatum*, a dimorphic fungus

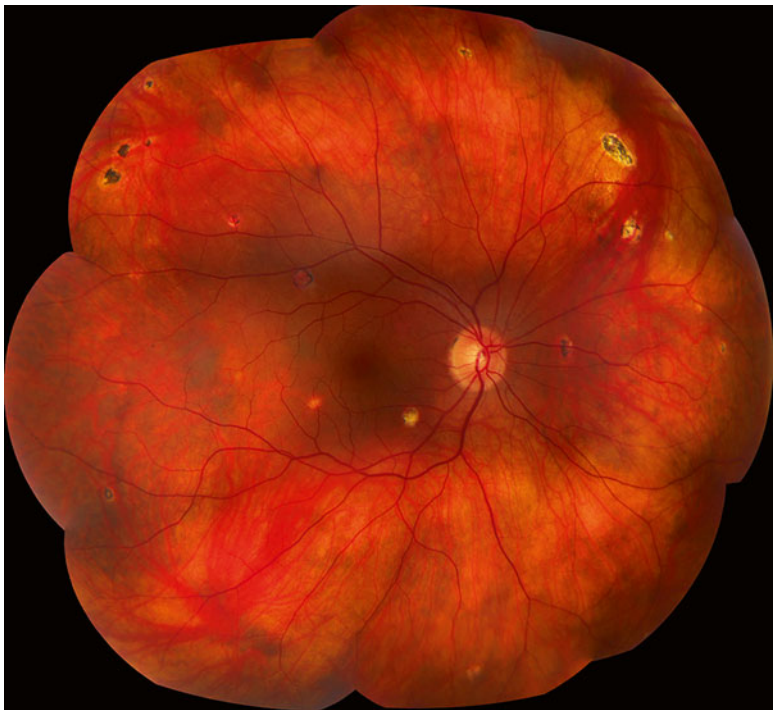

Fig. 24.10 Montage of right fundus of a patient with POHS. Note the mild peripapillary atrophy and scattered punched-out lesions in the posterior pole and periphery. Also note clear media and lack of vasculitis

that is endemic to the Ohio and Mississippi River Valleys [139–141]. Humans become infected by inhalation of spores, which then spread hematogenously to the spleen, liver, and uveal tract. Acute infection is typically self-limited and may be asymptomatic or resemble a viral illness [139]. POHS typically presents between the ages of 20 and 50; however cases have been reported in teenagers [139]. POHS is diagnosed clinically by identifying typical ophthalmoscopic findings including peripapillary atrophy and multiple, atrophic, choroidal scars ("histo spots") in the absence of vitritis (Fig. 24.10). The choroidal scars represent the dissemination of the organism to the choroid, resulting in choroidal granulomas; resolving granulomas then develop into focal areas of choroidal and RPE atrophy, leaving multiple, "punched-out" lesions [139].

The majority of patients with POHS are asymptomatic. However, the development of choroidal neovascularization (CNV) is a well-known sight-threatening complication that may occur at sites of atrophic scars, as a result of focal breaks in Bruch's membrane [140, 141].

Treatment for POHS is targeted at the CNV. Antifungal medication is not indicated as the organism is not present in the atrophic lesions [139]. Intravitreal anti-vascular endothelial growth factor (VEGF), photodynamic therapy, local corticosteroid injection, and photocoagulation have all been successfully used to treat CNV due to POHS.

Endogenous Endophthalmitis

Infectious endophthalmitis is a rare complication of septicemia, penetrating globe trauma, or intraocular surgery [142]. Endogenous infection, resulting from hematogenous spread of microorganisms to the eye, is the least common cause of infectious endophthalmitis in children. It accounts for only 0.1–4 % of all cases, with the highest incidence in India and the lowest in the USA [143, 144]. Risk factors for endogenous endophthalmitis in the pediatric and neonatal age group include prematurity, bacteremia, candidemia, prolonged hospitalization, and the presence of indwelling catheters [143, 145]. The most common etiology of fungal endophthalmitis is *Candida albicans*, and common causes of bacterial endophthalmitis include *Pseudomonas* species, group B *Streptococci*, and *Klebsiella* [145–147]. Although the incidence of endogenous endophthalmitis in children is rare, the ophthalmologist should have a high index of suspicion in susceptible patients, as delays in diagnosis can lead to poor visual outcomes. Patients may present with fulminant features such as eyelid edema, conjunctival injection and chemosis, and hypopyon, or the infection may affect only the posterior segment, manifesting as vitritis or retinal infiltrates [146]. Management of endogenous endophthalmitis includes parenteral antimicrobials, intravitreal injections, and vitrectomy [146].

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