Ocular Manifestations of Infectious Diseases

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Introduction

Many systemic infectious diseases have ophthalmic complications or associated eye findings. The goal of this chapter is to discuss the ophthalmic manifestations in infectious disease. Due to the exhaustive list of infections that affect the eye, there are some noteworthy omissions to this chapter. This chapter does not cover the plethora of infections that can cause preseptal or orbital cellulitis or diseases that alter the immune system and increase risk of infections, such as human immunodeficiency virus (HIV). Additionally, many of the pathogens known to cause endophthalmitis and conjunctivitis are not covered. Here we discuss the most common systemic diseases in which ocular complications can arise so that the pediatric ophthalmologist and treating pediatrician can provide the proper surveillance and treatment.

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Bacterial Diseases

Bartonella Henselae

Definition

Bartonella henselae is a gram-negative bacteria that causes a systemic infection, often referred to as Cat Scratch Disease. Antecedent scratch or bite, generally from a cat and occasionally from a dog, is reported in most patients and often recalled as a result of mild trauma occurring a week or two before illness begins [1].

Epidemiology

Exact incidence of Cat Scratch Disease is unknown. Serologic prevalence of *Bartonella henselae* in cats in the US ranges widely from 13 to 90 % [5]. The rate of pediatric hospitalizations from cat scratch disease has remained stable in the last 20 years [6]. Cat scratch disease is not transmitted from person to person [5] and is more common in children than adults [2].

Systemic Manifestations

Most patients with Cat Scratch Disease develop local lymphadenopathy and about one third develop a febrile illness, which is usually mild. Patients may also describe a papule or pustule at the scratch or bite site 1–2 weeks preceding the lymphadenopathy. Atypical manifestations of Cat Scratch Disease include prolonged fever, vertebral osteomyelitis, new onset status epilepticus, encephalopathy or encephalitis, osteolytic bone lesions, and granulomatous hepatitis. Immunocompromised individuals may present with a rare vasoproliferative disordered names bacillary angiomatosis, characterized by numerous vascular tumors of the skin and subcutaneous tissue. Another vasoproliferative disorder that can developed in immunocompromised patients is bacillary peliosis, which involves solid organs with reticuloendothelial elements, such as the liver or spleen [1].

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Cat-scratch disease is a common disease for pediatricians, although the actual incidence is unclear. CSD commonly presents with regional lymphadenopathy. Affected children can be quite ill with fever and malaise, or have minimal complaints. The enlarged lymph nodes drain the site of inoculation, both from scratches and bites. The lymphadenopathy generally occurs 1–3 weeks after bacterial inoculation, and may involve axillary, cervical, or inguinal nodes. Most patients have some systemic symptoms such as myalgias, arthralgias, malaise, chills and fever. The vast majority of cases are self-limited with a benign clinical course, but the enlarged lymphadenopathy may persist for several months. CSD generally resolved spontaneously, with or without treatment, in 1–2 months. However, on rare occasions, CSD can result in serious neurologic complications such as meningoencephalitis, encephalopathy and seizures or cardiac complications, specifically lethal endocarditis [1].

Ophthalmic Manifestations

Eye involvement with systemic *Bartonella henselae* infection is reported to be 3–10 % [2, 3] with a minority of those patients presenting with the classic neuroretinitis (2–3 %) [4]. Most patients who have eye involvement due to *Bartonella henselae* infection come to the attention of the ophthalmologist due to decreased vision in one or both eyes or complaints of eye pain. Some other symptoms include photopsias and floaters. Visual acuity can range from normal to very poor (counting fingers or worse) depending on the severity of the eye involvement. In the largest series of patients with cat scratch optic neuropathy, flu-like symptoms was most common complaint followed by headache, eye pain, and pain with eye movement [2].

Patients who have eye involvement complain of blurred vision usually in one eye though up to 17 % of cases have bilateral involvement [2]. Patients usually have had known contact with cats or kittens but often will just recall the scratch or bite in retrospect.

The most common ocular manifestation of a systemic Bartonella Henselae infection is optic neuropathy (63–90 %) [2, 7] followed by neuro retinitis (nerve edema with a macular star) [2]. Vitritis can occur in cat scratch disease, and other more rare complications include branch retinal vein occlusion and macular hole [2, 7].

The combination of optic nerve edema and macular edema are often described as neuro retinitis, and an also be seen in other disorders such as Lyme disease, sarcoidosis, Rocky Mountain spotted fever, malignant hypertension, and toxoplasmosis. Some patients do not develop the full neuro retinitis, but have isolated nerve edema, retinal whitening, vitritis, choroiditis, or focal retinitis [2]. The neuroretinitis in bartonella infection has been reported to be bilateral in about 17 % of cases [2]. The mechanism of the macular star is not known but thought to be secondary to an immune response [8].

Most (67[2]–74[7]%) patients who have cat scratch disease with ocular involvement have an excellent visual outcome yet it is unclear how much of a role, if any, antibiotic or steroid treatment has in the final vision.

Diagnosis

Culture is rarely useful for the diagnosis of *Bartonella henselae* due to its fastidious nature. Bartonella serology, IgG and IgM and/or polymerase chain reaction (PCR) may be used for diagnosis depending on the clinical scenario and specimen. Additionally histology from lymph biopsies can be helpful if epitheliod granuloma formation is present [5].

Management

For typical cat scratch disease without severe vision loss or lymphadenopathy in an immune competent patient, treatment may not be needed [9]. Management of neuro retinitis is controversial with many ophthalmologists in favor of treatment of all cases and some physicians feeling comfortable with observation since an immune competent patient should be able to heal without intervention [8].

For patients without eye involvement and without significant systemic illness or immunodeficiency, for whom the decision to treat is made, the current recommended treatment is azithromycin 10 mg/kg orally on day 1 and then 5 mg/kg orally from days 2 to 5. The standard treatment for adults with retinal involvement is doxycycline (100 mg PO bid) and rifampin (300 mg PO) for 4–6 weeks with the consideration of topical steroids [9]. There is no consensus on the treatment of children with retinal involvement of *Bartonella henselae* infection. Azithromycin, clarithromycin, trimethoprim-solfamethoxazole, doxycycline, fluroquinolones, gentamicin and rifamim all have activity against bartonella and can be used in certain clinical situations. Generally combination therapy is used for neurologic disease.

Lyme Disease

Definition

Lyme disease is a tick-born infection caused by the spirochete *Borrelia burgdorferi*. It is transmitted to humans from the bite of the *Ixodes* tick, also known as the deer tick or blacklegged tick [10]. Lyme infection in the eye is often referred to as a masquerade disease due to its variable presentation.

Epidemiology

Lyme disease is the most common vector-born disease in the U.S. [12]. In 2011, there were over 24,000 confirmed cases of Lyme disease in the U.S. It is most commonly seen in children between the ages 5 and 15, with a secondary peak in adults aged 45 and 55. Most cases present between

May and September [10]. It is endemic in multiple regions of the U.S., particularly the Northeast, upper Midwest, and Northwest [12].

Systemic Manifestations

Patients do not always have a known history of a tick bite or the typical erythema migrans rash in which case travel and activity history are useful. Systemic manifestations and travel history are what guide the clinician toward diagnosing Lyme disease as the cause of ocular disease. Ocular symptoms often include periocular or intraocular pain, photophobia, blurred vision, and floaters [11].

Systemic features include the characteristic "bulls-eye" rash that spreads slowly from the site of the tick bite, known as erythema migrans (EM). The rash is seen in about 90 % of patients and is often accompanied by a flu-like illness with headache, malaise, fever, and regional lymphadenopathy [13]. Disseminated disease presents with musculoskeletal and neurologic signs, including arthralgias, myalgias, cranial nerve palsies (most commonly facial nerve palsy), and meningitis. Carditis, causing heart block, is seen in <1 % of children [10]. In late disease, the most frequent manifestation is a chronic, episodic arthritis [14].

The CDC recognizes three stages of Lyme disease an early stage that occurs 3–30 days after the tick bite and is associated with the EM rash as well as fatigue, swollen lymph nodes, and generalized aches. In the days to weeks after the tick bite, the patient enters the early disseminated stage where additional areas of EM appear on the body, facial nerve palsies appear, and other symptoms such as severe headaches and neck pain due to meningitis, large joint pain and swelling, and heart palpitations may occur. The late disseminated phase occurs months to years after the tick bite and the patient experiences intermittent arthritis and chronic neurologic complaints such as short term memory problems and tingling in extremities [15].

Ophthalmic Manifestations

Ophthalmic findings can be seen in early or late disease [11]. A nonspecific follicular conjunctivitis is seen in approximately 11 % of patients with early disease and occurs within a few weeks of infection, and is the most common ocular finding in Lyme disease [11, 14, 16]. Stromal keratitis and episcleritis have been reported in late disease [13].

Intraocular inflammation can occur in both early and late disease [11, 16]. It can present with anterior uveitis, vitritis, choroiditis, and retinal vasculitis. Optic neuritis and neuroretinitis have also been described [14].

Seventh nerve palsies associated with Lyme can lead to an exposure/neutropic keratopathy. Other cranial nerve palsies (cranial nerve III, IV, and VI) will cause abnormalities in extraocular motility and diplopia [14].

Uncommonly, children with Lyme meningitis can develop a pseudotumor-cerebri-like syndrome causing elevated intracranial pressure and vision-threatening papilledema [10, 14].

Diagnosis of Lyme Disease

The CDC recommends a 2-step protocol for serologic diagnosis of active or previous infection: ELISA for IgM and IgG followed by Western immunoblot testing [15]. The clinician should keep in mind that an antibody response can take weeks to develop and may be transient, so a negative antibody test does not rule out disease. False positive testing can occur with infectious mononucleosis and autoimmune disease [10].

Direct DNA testing by PCR is of limited value in diagnosis because of lack of target DNA in clinical samples of blood or CSF [10].

Management

Children with localized erythema migrans or early disseminated disease without neurologic manifestations or without third-degree heart block should be treated with oral doxycycline (1–2 mg/kg BID) or amoxicillin (50 mg/kg/day divided in 3 doses) for 14–21 days [12]. Doxycycline is contraindicated in children <8 years of age. Patients with facial nerve palsy or first/second-degree heart block can also be treated with oral antibiotics as above.

Recommendations for the management of Lyme disease from the Infectious Disease Society of America do not include specific management based on eye findings and the route and duration of treatment has not been established for ocular disease. However, ocular involvement should be considered a central nervous system manifestation and treated with IV ceftriaxone (75–100 mg/kg/day in single dose) or cefotaxime (150–200 mg/kg/day in 3 or 4 doses) for 14–28 days in children [12].

Topical corticosteroids or mydriatics may be used to treat ocular inflammation and keratitis [13].

Syphilis

Definition

Syphilis is a systemic, bacterial diseased caused by the spirochete *Treponema pallidum.* It is transmitted by sexual contact or transplacentally from mother to fetus after the 10th week of pregnancy [17].

Epidemiology

Primary and secondary acquired syphilis account for 31 % of all cases, with the rest being either congenital or latent. The rate of primary and secondary syphilis more than doubled

between 2000 and 2013 from 2.1 per 100,000 to 5.3 per 100,000 people, with men accounting for 91 % of early cases in 2013 [19]. Ocular involvement occurs in about 10 % of secondary disease [17]. The rate of syphilis in men who have sex with men increased from 2000 to 2010 [20].

Congenital syphilis in the U.S. is related to late or no testing for syphilis during pregnancy.

Systemic Manifestations

Mothers of patients with suspected congenital syphilis and patients with suspected acquired syphilis may have a high-risk sexual history or a partner with high risk sexual behaviors. Ophthalmic symptoms are generally nonspecific and include pain, redness, photophobia, floaters, and visual impairment [18].

Syphilis can affect almost any organ or system in the body.

Untreated acquired syphilis is categorized into four stages: [17].

- Primary: Incubation period of 10–90 days. Characterized by non-tender, indurated, non-purulent chancre at the site of inoculation. Resolves spontaneously in 4 weeks.
- Secondary: 4–10 weeks following appearance of the chancre. Hematogenous dissemination of the spirochete causing neurologic, ophthalmic, gastrointestinal, and hepatic disease. A diffuse, maculopapular rash, prominent on the palms and soles is characteristic. Symptoms resolve without treatment.
- Latent: Asymptomatic period after resolution of secondary symptoms. Can last from months to a lifetime.
- Tertiary syphilis: 1/3 of patients progress to this stage. An obliterative endarteritis that can affect any organ in the body, most prominently cardiovascular and neurologic involvement (aortitis, neurosyphilis)

Systemic findings in early congenital syphilis (less than 2 years old) include: hepatosplenomeglay, changes in long bones on radiographic imagined, abdominal distension, desquamative rash, low birth weight, and pneumonia. Late manifestations (older than 3) include Hutchinson teeth, mulberry molars, abnormal facies, CNVIII deafness, saber shins, hard palate perforations, cutaneous lesions, and neuro syphilis [18].

Ophthalmic Manifestations

Ocular findings in syphilis are extremely variable. Anterior findings can include a papillary or granulomatous conjunctivitis, interstitial keratitis, episcleritis, or scleritis [17]. Corneal inflammation results in an immune-mediated, nonulcerative, stromal keratitis. Untreated, this keratitis can cause corneal neovascularization or scarring with ghost vessels. In the pre-antibiotic era most interstitial keratitis was associated with syphilis, 90 % with congenital syphilis [17]. Interstitial keratitis is the most common inflammatory finding in untreated late congenital syphilis. Interstitial keratitis, cranial nerve VIII deafness, and Hutchinson teeth is called the *Hutchinson triad* [18].

Syphilis can present as a nonspecific granulomatous or nongranulomatous anterior, intermediate, posterior, or pan uveitis. Posterior findings can include vitritis, chorioretinitis, retinal vasculitis, branch retinal vein occlusion, and serous retinal detachment. Optic nerve involvement includes disc edema, neuroretinitis, pallor, or an optic nerve gumma [19].

There are some clinical patterns that can allow rapid diagnosis on ophthalmic examination. In syphilitic panuveitis, patients may have preretinal, white opacities that migrate over the retina during the disease course and treatment. Another distinctive presentation is an acute, placoid chorioretinitis.

The Argyll Robertson pupil (miotic pupil with light-near dissociation) is mostly associated with late disease [17].

In congenital syphilis, ocular inflammatory disease can be present at birth or can present decades later. A multifocal choroiditis and retinal vasculitis are the most frequent uveitis manifestations. Patients can also have a pseudoretinitis pigmentosa picture caused by secondary degeneration of the RPE [18]. Congenital glaucoma and cataracts are also associated with congenital syphilis [17].

Diagnosis

Treponomal serologic testing is valuable for diagnosis. The CDC currently recommends enzyme immunoassays (EIAs) and chemiluminescent immunoassays (CIAs) to detect antibodies to treponemal antigens as the best screening tests for syphilis followed by reflex testing of positive specimens with the nontreponemal test, rapid plasma reagin (RPR). Syphilitic uveitis can also be directly diagnosed by PCR of aqueous humor [19].

Positive serologic testing in a patient with ophthalmic disease warrants CSF testing [19].

Management

Ocular syphilis is treated as neurosyphilis, with parenteral penicillin G being the treatment of choice. Ocular inflammation usually subsides with penicillin treatment [19].

Steroids have an adjuvant role in treating ocular inflammation. Topical steroids can be used to treat interstitial keratitis and anterior uveitis. Systemic steroids can be used in posterior uveitis, optic neuritis, and scleritis [19].

Chlamydia Trachomatis

Definition

Chlamydia trachomatis is a gram-negative, obligate intracellular bacterium. Urogenital infection is typically caused by serotypes D-K whereas serotypes A-C cause trachoma; an eye disease transmitted by direct exposure to the bacteria

often secondary to poor hygiene in developing countries. Urogenital serotypes of C. *trachomatis* can be passed to infants via perinatal exposure to the mother's infected cervix during birth [21, 22].

Epidemiology

Sexually active women <25 years of age are at high risk for chlamydial infection from C. *trachomatis* serotypes D-K [21]. The risk of transmission to infants of infected mothers is estimated to be between 50 and 75 %. Neonatal conjunctivitis is the most common clinical manifestation and is seen in 20–50 % of infected infants [23].

Trachoma is a blinding condition caused by repeated infection with *C. trachomatis* (serotype A–C) principally in resource-poor areas in developing countries. Transmission is through direct exposure to the bacterium in contaminated water and houseflies. It is the most common cause of infectious blindness worldwide. Trachoma is endemic in some of the poorest areas of Africa, Asia, Australia, and the Middle East, with 21 million people affected and 2.2 million blind or severely visually impaired worldwide. Active trachoma is most common in children <5 years of age [22].

Systemic Manifestations

Patients with Chlamydial infections of the eye caused by serotypes D-K usually present with unilateral, but occasionally bilateral irritated and red eye. Patients sometimes complain of blurred vision and usually complain of watery discharge. Genital infection is often asymptomatic.

Serotypes A-C cause an indolent infection usually beginning with foreign body sensation and tearing, sometimes with eye pain when patients have associated entropion, subsequent corneal scarring, and finally resulting in decreased vision, which can be very poor.

In addition to ocular findings, chlamydial infection from serotypes D-K in infants can cause a subacute, afebrile pneumonia around 1–3 months of age if left untreated. Characteristic presentation of chlamydial pneumonia includes a staccato cough with tachypnea, hyperinflation and bilateral infiltrates on chest X-ray. Chlamydia can also infect the urogenital or rectal mucosa, although infection is often asymptomatic in these locations [21].

Ophthalmic Manifestations

Ophthalmia neonatorum is conjunctivitis in newborns with onset <30 days after birth. *Chlamydia trachomatis* is the most frequently identified cause of ophthalmia neonatorum, which typically presents between 5 and 12 days of age as an acute, mucopurulent, papillary, conjunctivitis which may have pseudomembranes [21].

Chlamydia conjunctivitis can also present at older ages, often in sexually active teenagers and adults. In these cases, patients present with a chronic follicular conjunctivitis.

As noted earlier, trachoma is a blinding eye disease caused by repetitive ocular infection by *C. trachomatous* in developing countries. Active trachoma is characterized by a severe follicular conjunctivitis. Once active inflammation wanes, patients develop significant conjunctival scarring, eyelid distortion, entropion with trichiasis causing corneal damage that can progress to blindness. Classic manifestations of trachoma include Arlt's line, a thick horizontal line of scar tissue seen on the palpebral conjunctiva, and Herbert's pits, cicatrized limbal follicles seen on the cornea [22].

Diagnosis

In infants, diagnosis is confirmed by culture and nonculture tests, such as direct fluorescent antibody testing from specimens from conjunctival swabs. Conjunctival cells should be obtained from the everted eyelid using a Dacron tipped swab. The specimen must contain conjunctival cells, not just exudate. The specimen should also be tested for *Neiserria gonorrhea* co-infection [21].

Trachoma is principally a clinical diagnosis and laboratory confirmation is not necessary [22].

Management

Prenatal screening of pregnant women and treatment with azithromycin prior to delivery prevents the vertical transmission of Chlamydia serotypes D-K to infants. Neonatal ocular prophylaxis with silver nitrate or erythromycin ointment does not prevent ophthalmia neonatom caused by *C. trachomatis*, but should still be given as it prevents gonorrheal conjunctivitis [21].

In cases of neonatal conjunctivitis secondary to Chlamydia, treatment is warranted in both the child and the mother. Topical treatment alone in infants is not sufficient due to the risk of developing pneumonia. Infants are systemically treated with oral erythromycin 50 mg/kg/day divided into 4 doses daily for 14 days. Patients require close follow-up as treatment initial treatment with erythromycin approximately 80 % effective and a second course of antibiotic treatment may be required [21].

Patients with sexually transmitted Chlamydia also need to be treated systemically, and in these cases a single dose of oral azithromycin is recommended [21].

For trachoma, the World Health Organization recommends mass drug treatment in areas where the prevalence of follicular conjunctivitis is >10 %. The treatment of choice is a single oral dose of azithromycin (20 mg/kg). Topical tetracycline is given for 6 weeks. Surgical intervention is also recommended to correct clinically significant entropion and trichiasis. Along with antibiotic and surgical intervention, facial cleanliness and environmental improvements are also stressed to address the root cause of repeated infection [22, 24].

Gonococcal Infections

Definition

Gonococcal disease is caused by *Neisseria gonorrhea*, a gram negative diplococcus. Gonorrhea is primarily a sexually transmitted disease. It is transmitted vertically to infants by exposure to the mother's infected cervix.

Epidemiology

Humans are the only reservoir of gonorrhea [25]. In the U.S., approximately 700,000 new cases of gonococcal infection are reported each year. It is the second most common sexually transmitted disease, behind chlamydial infection [26].

Systemic Manifestations

The infected neonate can present with meningitis, sepsis, scalp abscesses, septic arthritis, and wound infections. Less commonly they may develop a vulvovaginitis, proctatis, rhinitis, and urethritis. Blood and CSF cultures should be obtained in infants with ocular infection due to the risk for sepsis and meningitis [25].

Ophthalmic Manifestations

Neonates will present with a purulent conjunctivitis at 2–4 days of life. Often eyelid edema is present. A history of gonorrhea in one or both parents can often be elicited.

The most common manifestation of gonococcal infection in infants is ophthalmia neonatorum. It can range from a mild to a severe, rapidly destructive conjunctivitis causing corneal scarring and blindness. It can occur earlier with premature rupture of membranes. Infants will present with bilateral, mucopurulent, and sometimes bloody discharge with eyelid edema and chemosis. Severe cases can lead to corneal ulcers, corneal perforation, and panophthalmitis [25]. Sexually active adolescents can also get a severe mucopurulent conjunctivitis from direct contact with infected secretions (Fig. 12.1).

Diagnosis

For ocular disease, culture from conjunctival exudates is the gold standard for diagnosis of gonoccal infections. Colonies grow within 24–48 h of inoculation but generally gonorrhea tends to be difficult to culture. It is important to plate the secretions immediately onto chocolate agar for best results [5]. Gram stain as has good sensitivity for gonococcal infection, but does not confirm diagnosis. Nucleic acid amplification tests (NAATs) are useful for urogenital infection [5].

Management

A single IM dose of ceftriaxone is the treatment of choice for gonococcal ophthalmia neonatorum, along with eye irrigation with saline solution at frequent intervals until the discharge has resolved. Topical antibiotic treatment is unnecessary when systemic treatment is given [25].

Fig. 12.1 Purulent conjunctivitis due to gonorrhea infection

In the United States, prophylaxis for gonococcal ophthalmia neonatorum is recommend in all infants and required by law in many states. Medication is applied topically within 1 h after birth. Prophylactic medications include 1 % silver nitrate solution, 1 % tetracycline ointment, or 0.5 % erythromycin ointment, however topical silver nitrate and tetracycline are no longer manufactured in the U.S. [25, 26]. Infants born to mothers with known gonococcal infection should be treated with a single parenteral dose of a 3rd generation cephalosporin due to the potential for failure of prophylaxis [25].

Leprosy

Definition

Leprosy, also known as Hansen's disease, is a chronic, granulomatous infectious disease caused by the acid-fast bacillus *Mycobacterium leprae.* The bacterium is transmitted from person-to-person through droplet exposure. It is a slowly replicating bacterium, with an incubation period of about 5 years. It can take up to 20 years for symptoms of the disease to actually appear. Leprosy is disease of the skin, peripheral nerves, and mucus membranes caused by infiltration of the bacterium in these locations [27].

Epidemiology

Worldwide, 200,000–300,000 patients are blind from leprosy [28]. At the end of 2012, official figures from 115 countries reported a registered global prevalence of leprosy at 189,018 with 232,857 new cases reported during the same year. Leprosy is exceedingly rare in the United States, but is highly endemic in the following countries: Angola, Bangladesh, Brazil, China, Democratic Republic of Congo, Ethiopia, India,

Indonesia, Madagascar, Mozambique, Myanmar, Nepal, Nigeria, Philippines, South Sudan, Sri Lanka, Sudan and the United Republic of Tanzania [27]. Even in highly endemic areas, the bacterium has low pathogenicity. Only 5 % of people exposed to the bacterium eventually develop disease. The remaining 95 % show resistance to the disease [29].

Systemic Manifestations

Clinical manifestations of leprosy depend on the patient's immune response. There are two clinical forms of leprosy, lepromatous and tuberculoid, however patients can also have overlap between these two types. In tuberculoid leprosy, patients have a vigorous cellular immune response that limits the disease to a few, defined skin patches or nerve trunks. In lepromatous disease there is an absence of a specific cellular immune response to the bacterium, thus allowing for uncontrolled proliferation of the bacterium resulting in many lesions and extensive infiltration of the skin and nerves [30].

Skin lesions most commonly manifest as hypopigmented, and sometimes erythematous, macules or plaques with a raised edge, often with reduced sensation. Nerve infiltration and damage occurs in the peripheral nerve trunks and the small dermal nerves. Involvement of nerves causes nerve enlargement, with or without tenderness, and regional patterns of sensory or motor loss. Small dermal and autonomic nerve involvement causes hypoaestheisa, anhidrosis, and can cause a stocking-glove sensory loss [30].

Ophthalmic Manifestations

Along with systemic findings, patients with leprosy involving the eye will present with reduced visual acuity or even blindness [27].

Leprosy affects the eye through direct infection of the bacterium in the skin of the eyelids, tear ducts, and lacrimal glands, facial nerve, ophthalmic division of the trigeminal nerve, or direct invasion of the anterior segment [28].

Adnexal manifestation includes madarosis of the eyelashes and eyebrows, lagophthalmos (due to facial nerve infiltration), entropion, ectropion, trichiasis, and low lacrimal secretion. Anterior segment findings include conjunctivitis, decreased corneal sensation (due to trigeminal nerve involvement), exposure keratitis, corneal opacities, iris nodules, iris atrophy, anterior uveitis, episcleritis, and scleritis [28, 29]. Thickening and beading of corneal nerves is detected on slit lamp exam and is a common and characteristic finding in early leprosy [31]. The posterior segment involvement, very rare in leprosy, manifests as minute, white, "pearl-like" choroidal nodules, similar to those seen in the iris [29, 31].

Diagnosis

Diagnosis of leprosy is principally based on clinical signs and symptoms. Smears of affected skin can be performed to detect the presence of acid-fast bacilli. In endemic regions, a patient is regarded as having leprosy if he or she has the following:

1. Hypopigmented or reddish skin lesions with loss of sensation
2. Involvement of the peripheral nerves, indicated by loss of sensation and weakness in the muscles of the hands, feet, or face
3. Skin smear positive for acid-fast bacilli [27]

Management

For treatment purposes, leprosy is classified as multibacillary (more than 5 lesions), puacibacillary (2–5 lesions), or a single-lesion disease [30].

The World Health Organization recommends a multidrug antibiotic regimen for the treatment of leprosy, which includes a combination of rifampin, clofazamin, and dapsone for 12 months in patients with multibacillary leprosy or a combination of rifampin and dapsone for 6 months in patients with paucibacillary leprosy. Patients with single lesion leprosy can be treated with a one-time dose of rifampin, ofloxacin, and minocycline taken together [27].

Facial nerve paralysis causing lagophthalmos with onset within 6 months can be treated with oral corticosteroids. The patient should be instructed to tape the eyelids closed, lubricate corneal and consider an eye patch/shield to protect the eye for exposure. Uveitis should be treated with topical corticosteroids and mydriatics. Corneal abrasions, keratitis, or ulcers caused by exposure should be treated as usual with lubrication and topical antibiotics [27].

Tuberculosis

Definition

Tuberculosis (Tb) is a chronic, granulomatous infection caused by the acid-fast bacillus *Mycobacterium tuberculosis* [32]. The bacterium is most commonly transmitted by aerosolized droplets [33].

Epidemiology

The World Health Organization estimates approximately one-third of the world population is latently infected with Tb, with >9 million cases of active tuberculosis yearly [33]. China, India, and the African continent account for the largest number of new and recurrent cases. The incidence of tuberculosis in the United States in 2011 was 3.4 cases per 100,000 people, with immigrants and ethnic minorities being disproportionately affected. The highest incidence in the U.S. is among Asians. Approximately 79 % of foreign-born people with Tb were diagnosed after being in the U.S. more than 2 years, consistent with reactivation of latent disease. In the U.S., tuberculosis has

reemerged as a public health problem due to the AIDS epidemic [32]. Eighty-one percent of those diagnosed in 2011 were HIV-positive [34].

Uveitis due to systemic Tb infection varies around the world. Eye involvement in patients with systemic Tb ranges from 0.14 to 10 % of patients with Tb in India, 1 % in the United States, 4 % in China, 6 % in Italy, 7 % in Japan, and 16 % of patients in Saudi Arabia [33].

Systemic Manifestations

Systemic disease can occur after primary exposure, but in 90 % of cases it occurs secondarily after reactivation of the disease. The great majority of patients mount an immune response upon initial infection leading to the formation of pulmonary caseous granulomas that contain, but do not eliminate, the infection. A small proportion of the bacteria live in a dormant state within these granulomas and can be reactivated later in life. In an immunocompetent individual, the risk of reactivation is 10 % over the course of a lifetime. The risk of reactivation is even higher, 10 % yearly, in a patient with HIV [33].

The most common manifestation of reactivated tuberculosis infection is granulomatous lung disease, seen in 80 % of patients with reactivation. Extra-pulmonary tuberculosis can manifest in the gastrointestinal tract, cardiovascular system, musculoskeletal system, genitourinary system, central nervous system, as well as the eyes [32]. Miliary Tb most commonly occurs in immunocompromised patients, and represents unchecked hematogenous dissemination of the infection in primary or secondary disease.

Ophthalmic Manifestations

Ocular manifestations of Tb can result from active infection or from an immunologic reaction to the organism [32]. Tuberculosis can affect the anterior and posterior segment of the eye, as well as the orbit. Presentation of Tb is extremely varied and it can present as an acute anterior uveitis, chronic granulomatous anterior uveitis with mutton fat keratic precipitates, an intermediate uveitis, vitritis, macular edema, retinal vasculitis, neuroretinitis, multifocal choroiditis, subretinal abscess, endophthalmitis, and panophthalmitis [32]. Tb has also been associated with necrotizing and non-necrotizing diffuse or nodular scleritis, epscleritis, and peripheral ulcerative keratitis. Rarely, Tb associated inflammation presents as an interstitial keratitis, phylyctenulosis, iris or ciliary body granulomas, and dacroadenitis [34]. Among these manifestations, the most common clinical finding is posterior uveitis [32, 34]. Eales disease, classically thought to be an idiopathic retinal vasculitis, is now considered to represent a hypersensitivity reaction to tuberculous antigens. It is characterized by a peripheral ischemic vasculitis with neovascularization and recurrent vitreous hemorrhage without other signs of inflammation, and is typically seen in young men where tuberculosis is endemic [33].

Tuberculous choroidal granulomas (tuberculomas) occur in association with pulmonary and non-pulmonary systemic disease. They are usually white, cream, or yellow in appearance and can be unifocal or multifocal. Visual symptoms depend on location and extent of the tuberculomas. Systemic symptoms such as fever, malaise, cough, hemoptysis, and weight loss are helpful in alerting the clinician toward TB as the cause [34].

Diagnosis

A tuberculin skin test (TST) or serum quantiFERON-TB Gold testing can help aid in the diagnosis of ocular tuberculosis. However, neither of these tests is diagnostic for tuberculosis eye disease and the clinician must rule out other potential infectious or inflammatory causes of uveitis (such as sarcoidosis) on the differential before designating a diagnosis of ocular Tb. The gold standard for diagnosis of ocular Tb is a positive culture from ocular tissue or fluid, although this may be difficult to obtain in many cases. PCR testing on ocular tissue or fluid for Tb has low sensitivity, possibly due to a low bacterial load in ocular fluids and a thick cell wall of *M. tuberculosis* [34]. Chest X-ray or chest computed tomography can help in the cases of suspected ocular TB as it can reveal pulmonary lesions and lymphadenopathy [32].

Fluorescein angiography has an important role in the evaluation of a patient with suspected ocular tuberculosis. It is very sensitive in picking up evidence of retinal vasculitis, and often shows that vasculitis is more extensive than indicated by clinical examination. Macular edema, optic disc edema, and choroiditis are other potential angiographic findings [32].

Management

Treatment for ocular Tb is directed at both the inflammatory and infectious components of the disease. Multi-drug therapy with isoniazide, rifampin, ethambutol, and pyrazinamide initially for 2 months, followed by rifampin isoniazide for an additional 4–7 months is recommended. Systemic corticosteroid therapy (oral prednisone at 1 mg/kg/day) and topical steroids and cycloplegics are used in conjunction with antimicrobial therapy to treat the inflammatory response [32].

Group B Streptococcal Infections

Definition

Group B streptococcus, also known as *Streptococcus agalactiae,* is a gram positive cocci that is a major infectious cause of neonatal obidity and mortality. In the U.S., universal screening guidelines have been in place by the CDC since 2002 to identify mothers to receive intrapartum antibiotics in

order to reduce the transmission of the bacteria to neonates and reduce the neonatal infection [35]. Pregnant women are routinely screened for GBS colonization between 35 and 37 weeks of gestation. If testing is positive, they are treated with intravenous antibiotics during delivery [36].

History Related to Eye Findings

Ocular infection with GBS is extremely rare in neonates. Neonates with ocular involvement of GBS will have mothers who tested positive on screening prenatally. Most cases present with coincident sepsis or meningitis. Patients may present with conjunctival injection, periorbital edema/erythema, corneal edema or opacity, elevated intraocular pressure, iris neovascularization, or leukocoria mimicking retinoblastoma [36].

Epidemiology

Prior to perinatal preventative strategies, the incidence of early-onset neonatal infection with group B strep was 0.47/1000 live births (between 1991 and 2001). It has since declined to about 0.3/1000 live births in the following years. Despite this reduction, neonatal GBS is still the leading cause of serious neonatal infection resulting in significant morbidity and mortality [35].

The GBS colonization rate in pregnant women varies from 15 to 35 %. Risk factors for neonatal infection include positive vaginal cultures in the mother, bacteriuria during pregnancy, low-birth weight, preterm gestation, rupture of membranes >18 h, intrapartum fever, chorioamnionitis, previous infant with GBS disease, intrauterine fetal monitoring, and low levels of maternal anticapsular antibody [35].

Systemic Manifestations

Group B strep is a major cause of neonatal infection. It can present as an early-onset sepsis in the first days of life as well as a late-onset sepsis, which is into the first month or two of life. Presenting features of infants with GBS sepsis include respiratory distress or apnea, lethargy, refusal to feed, temperature instability, poor perfusion, hyperbilirubinemia, skin rash, pneumonia, or meningitis [35].

Ophthalmic Manifestations

Most patients with ocular tuberculosis have no manifestation of systemic or pulmonary disease [32]. Ocular symptoms are varied and depend on the part of the eye that is involved. Patients can present with visual changes, pain, photophobia, and tearing [33].

GBS ocular infection presents as endogenous endophthalmitis. As of 2010, there were only 6 reported cases of GBS endogenous endophthalmitis in neonates reported in the literature. In 4 of these reported cases, the infant was also diagnosed with GBS meningitis [36].

Diagnosis

Diagnosis of GBS endophthalmitis can be confirmed through vitreal culture. It most reported cases, it was presumed as these patients either had confirmed GBS sepsis or meningitis through blood and CSF cultures, respectively [36].

Management

As GBS endophthalmatis in neonates is very rare, there is no defined protocol for treatment. The few reported cases infants have been treated in varying ways. Nearly all infants were treated with systemic, intravenous antibiotics, which included a broad-spectrum penicillin and an aminoglycoside. Many also received intravitreal injection with vancomycin and ceftazidime. In cases where retinoblastoma could not be ruled out or the patient had a blind, painful eye, the eye was enucleated [36].

Parasites

Baylisascaris Infections

Definition

Baylisascariasis is caused by infection by the nematode parasite *Baylisascaris procyonis.* The definite host for this parasite is the American raccoon. Infection occurs in humans after consumption of the parasite egg, which hatches in the intestine. Hatched larvae penetrate the gut wall and migrate to other organs after entering the blood stream through the portal system [37].

Epidemiology

Baylisascaris is indigenous in North American raccoons, but occurs in raccoons all across the world. In North America, the prevalence of *Baylisascaris* in raccoons is highest in the Midwest, northeast, and West Coast raccoon populations [37].

The most important risk factors for infection include pica or geophagia, and exposure to raccoons or environments contaminated with raccoon feces, which contain the parasite eggs [37].

Baylisascaris is the most common cause of diffuse unilateral subacute neuroretinitis (DUSN) though other nematodes have been described to cause DUSN including *Toxocara* spp. or *Ancylostoma* spp. [37, 39].

Systemic Manifestations

Infection of organs other than the eye and heart is known as visceral larva migrans (VLM), and is caused by migration of hatched larva to various organs of the human body. Infection causes granuloma formation, which have histologically been found in the heart, mediastinal soft tissues, pleura and lungs,

small and large bowel walls, and mesentery and mesenteric lymph nodes. Presentation includes nonspecific clinical findings such as a macular rash most commonly on the face and trunk, hepatomegaly, and pneumonitis with dyspnea and tachypnea [37].

In its most severe form, *B. procyonis* is a rare cause of fatal or neurologically devastating neural larva migrans (NLM) in infants and young children, characteristically presenting as an acute, fulminant eosinophilic meningoencephalitis [37].

Ophthalmic Manifestations

Patients infected with *Baylisacaris* will present with diffuse unilateral subacute neuroretinitis (DUSN) and complain of progressive visual impairment, often unilateral. In those with isolated ocular disease, there is commonly no known exposure to raccoons or raccoon feces, indicating that disease occurs after ingestion of a small number of eggs followed by chance migration of a single larva to the eye [37].

DUSN can have an insidious onset. Early symptoms may include a unilateral paracentral or central scotoma, pain, discomfort, or transient visual obscurations. Patients usually have good general health [38].

Ocular disease (Ocular larva migrans, OLM) occurs in both adults and children. It can be an isolated finding or associated with NLM and VLM [37].

Most infants and children with NLM or VLM can develop visual impairment or blindness from invasion of larva into the visual cortex or into the eye itself [37].

Patients with DUSN have a variety of findings that can cause visual loss including vitritis, choroidioretinitis, optic neuritis or atrophy, papillitis, and crops of multiple evanescent, gray-white outer retinal lesions. In the late stages, optic atrophy, retinal artery narrowing, diffuse pigment epithelial degeneration, and an abnormal electroretinogram can be seen [40]. Late features of DUSN can include retinal narrowing, optic nerve atrophy, and focal or diffuse retinal pigment epithelium atrophy [38]. Ophthalmic exam can sometimes reveal a migrating larvae within the retina (Fig. 12.2). Visible *Baylisascaris* in the retina is larger in size than *Toxocara*, another common cause of OLM (1000–2000 × 60–70 μm vs. 350–445 × 20 μm, respectively).

Eighty percent of patients with late stage DUSN have profoundly decreased vision at 20/200 or worse [40].

Diagnosis

Diagnosis is mainly clinical, based on signs/symptoms, along with evidence of eosinophilia. Serologic testing showing the presence of anti-Baylisascaris antibodies in the CSF or serum is supportive of the diagnosis [37].

Management

OLM and DUSN have both been successfully treated with laser photocoagulation of the intraretinal larvae, however the worm is only visualized in 25–40 % of cases [41]. Systemic steroids are used to reduce any sequential intraocular inflammation. There is no one drug proven to be effective in treating Baylisascariasis [5]. The role of anti-helminthics in ocular disease has not been established [37].

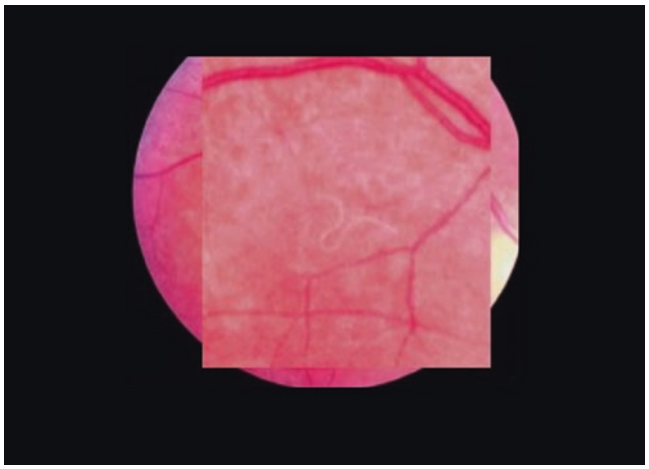

Fig. 12.2 Subretinal larvae seen in DUSN (photo courtesy of Scott Oliver, MD)

Toxocariasis

Definition

Toxocariasis is a parasitic infection caused by the roundworm species *Toxocara.* The definitive host of this species is the common house cat (*Toxocara cati*) and dogs (*Toxocara cani)*. Infection in humans occurs after ingestion of material contaminated with parasite eggs. The eggs hatch in the intestines then migrate to tissues throughout the body [42].

Epidemiology

Ocular *Toxocara* primarily affects children, with geophagia and dog-ownership being significant risk factors. Most children present in late childhood or in adolescence [42].

Systemic Manifestations

As with *Baylisascaris* infection, systemic infection with *Toxocara* is also termed visceral larva migrans (VLM). Systemic disease is characterized by fever, malaise, hepatomegaly, rash, and leukocytosis [42].

Ophthalmic Manifestations

Patients usually present with monocular visual loss. Visual acuity can be severe, as low as 20/200 or less in many cases. Toxocariasis is an important diagnosis to consider in patients who present with leukocoria and can have presentation similar to retinoblastoma. The most common clinical findings include diminished vision, leukocoria, vitritis, ocular injection, and strabismus [42].

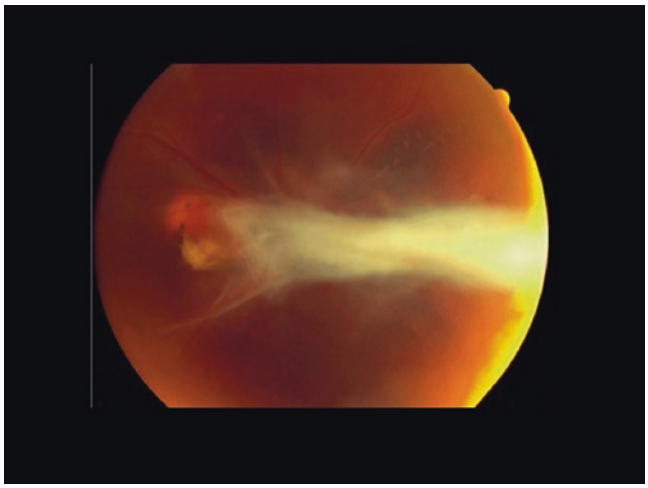

Fig. 12.3 White, posterior pole granuloma in patient with toxocariasis (photo courtesy of Scott Oliver, MD)

Toxocara is another parasitic infection that causes ocular larva migrans (OLM), which occurs when the parasite infiltrates the eye and causes and inflammatory reaction. It occurs unilaterally in 90 % of cases.

Clinical presentation can be classified into four forms: a posterior pole granuloma, peripheral granuloma, nematode endophthalmitis, or an atypical presentation. The posterior pole granuloma is the most common form of presentation (Fig. 12.3), and is characterized by a focal, whitish subretinal or intraretinal inflammatory mass in the posterior pole, with or without signs of acute inflammation. Peripheral granulomas appear as focal, white, elevated nodules in the periphery, which may have surrounding inflammatory membranes or pigmentary changes.

Toxocara endophthalmitis is a panuveitis and involves a prolonged course of inflammation caused by the intraocular nematode. It manifests as a red, painful eye with diffuse inflammation, and retinal exam may reveal a granuloma and tractional inflammatory membranes.

Atypical presentations include papillitis, optic nerve head edema, motile subretinal larvae, diffuse chorioretinitis, conjunctivitis, keratitis, iridocyclitis, focal iris nodules, and cataract [43].

Diagnosis

Serologic testing with ELISA for the *Toxocara* excretory secretory IgG has a reported 90 % sensitivity and specificity for systemic infection. ELISA studies can be performed on aqueous or vitreous samples as well. However, ocular toxocariasis is primarily a clinical diagnosis, and only histopathologic evaluation of an enucleated eye will reveal larvae [42].

Management

Ocular inflammation is routinely managed with topical, periocular, or systemic corticosteroids. Cycloplegics may be used if anterior segment inflammation is present. The need for systemic antihelmenthics is unclear. However, the use of antihelminthic drugs, such as albendazole, in combination with corticosteroids has shown favorable outcomes in some studies [43]. Vitreoretinal surgery is indicated in patients with retinal detachments caused by tractional membranes [42].

Toxoplasmosis

Definition

Toxoplasmosis is infection caused by the protozoan *Toxoplasma gondii*. Felines are the primary host of *T. gondii*. The organism is transmitted to humans orally after handling or eating raw meat that harbors tissue cysts or by drinking water or contaminated food with parasite oocysts. Congenital infection occurs through vertical transmission from an acutely infected mother transplacentally to the fetus. The risk of congenital toxoplasmosis is highest in the third trimester, whereas clinical manifestations are more severe if acquired during the first trimester [44].

Epidemiology

In 2004, it was estimated that that up to one-third of the world's population was infected with *Toxoplasma gondii*; however, there is significant geographic variation in seroprevalance. Prevelance of *T. gondii* IgG positivity among U.S. born subjects between 1999 and 2004 was estimated to be about 9 %. Multiple studies performed in various countries have identified toxoplasmosis as the most common cause of posterior uveitis [44].

The incidence of congenital toxoplasmosis varies geographically. In the U.S., it is estimated to occur in 1 in 10,000 live births, with the incidence ocular disease being reported to be as high as 75–94 % of these cases. Ocular disease is the most common manifestation of congenital toxoplasmosis [44].

Systemic Manifestations

Immunocompetent people who acquire toxoplasmosis usually do not have any other systemic findings other than asymptomatic cervical lymphadenopathy. Roughly 10 % of otherwise healthy people who are infected with toxoplasmosis will report non-specific symptoms such as myalgias, fevers, and fatigue. Infection in immunocompromised individuals most commonly presents as a fatal encephalitis, but may also manifest as a pneumonitis or septic shock [45].

Congenital toxoplasmosis can cause spontaneous abortion, or the child may be born with hydrocephalus, microcephaly, intracranial calcifications, epilepsy, psychomotor retardation, and leukopenia [45] (Fig. 12.4).

Ophthalmic Manifestations

The most common clinical presentation of toxoplasmosis is eye involvement, presenting as a retinochoroiditis [44]. The classic finding ocular finding is a fluffy, white area of

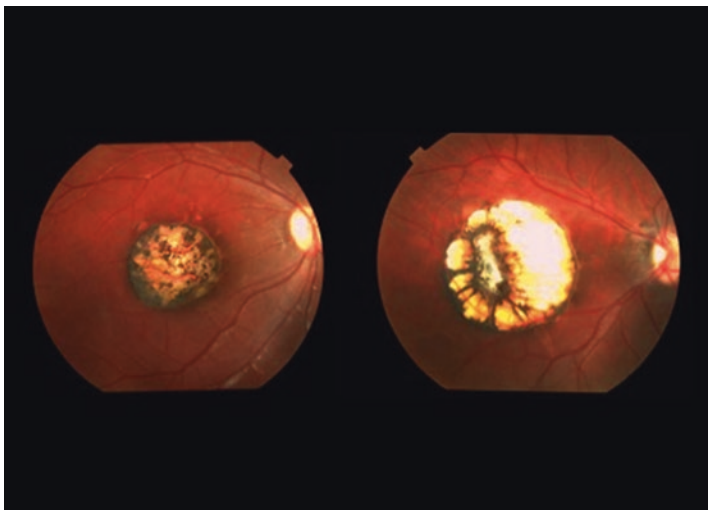

Fig. 12.4 Macular scarring seen in congenital toxoplasmosis (photo courtesy of Scott Oliver, MD)

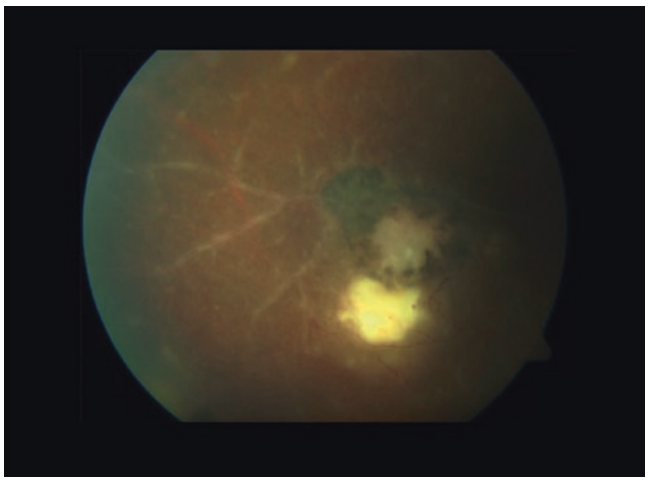

Fig. 12.5 Classic white area of retinitis adjacent to chorioretinal scar in reactivated toxoplasmosis (photo courtesy of Scott Oliver, MD)

retinochoroiditis or necrotizing retinitis adjacent to a chorioretinal scar (Fig. 12.5). Patients will typically also have a vitritis, causing a "headlight in the fog" appearance. Atypical presentations can manifest as retinal vasculitis, granulomatous or nongranulomatous anterior uveitis, or papillitis [45]. Ocular disease may be asymptomatic in young children. Verbal children may note decreased vision or eye pain, while parents may notice leukocoria or strabismus [45].

Diagnosis

In the majority of cases, the diagnosis of ocular toxoplasmosis is made by observation of the classic clinical findings described above. PCR or antibody testing can be performed on ocular fluid in atypical or unclear cases. Serologic testing for *T. gondii* antibodies has little role in the diagnosis of ocular toxoplasmosis due to high rate of seropositivity in the general population [45].

Management

With or without treatment, the active retinochoroiditis caused by toxoplasmosis resolves within 1–2 months in immunocompetent individuals. There is currently no drug available that is known to completely cure infection in humans. Thus, the goal of antimicrobial therapy is to limit parasite replication in active retinochoroiditis. Most ophthalmologists will treat patients with reduced vision, a lesion located within the arcades or near the optic disc, or those with significant vitreous haze. Infection in immunocompromised patients and atypical presentations also warrant treatment. The classic treatment includes pyrimethamine orally, sulfadiazine, and systemic corticosteroid. Folinic acid should be used to avoid toxicity related to pyrimethamine. An alternative treatment option is trimethoprim-sulfamethoxazole and systemic corticosteroid. Corticosteroids should be omitted in immunocompromised patients, and these patients should remain on prophylactic therapy (often with trimethoprim-sulfamethoxazole) while in an immunocompromised state [45].

Cysticercosis

Definition

Cysticercosis is a parasitic infection caused by the pork tapeworm, *Taenia solium.* The parasite exists as a cyst in pig, the intermediate host, and as worm in humans, the definitive host. Humans become infected after eating raw pork or consuming water or food contaminated with fecal matter [46]. Ingested eggs hatch in the intestines, migrate across the intestinal wall into the blood stream or lymphatic system. The parasite travels

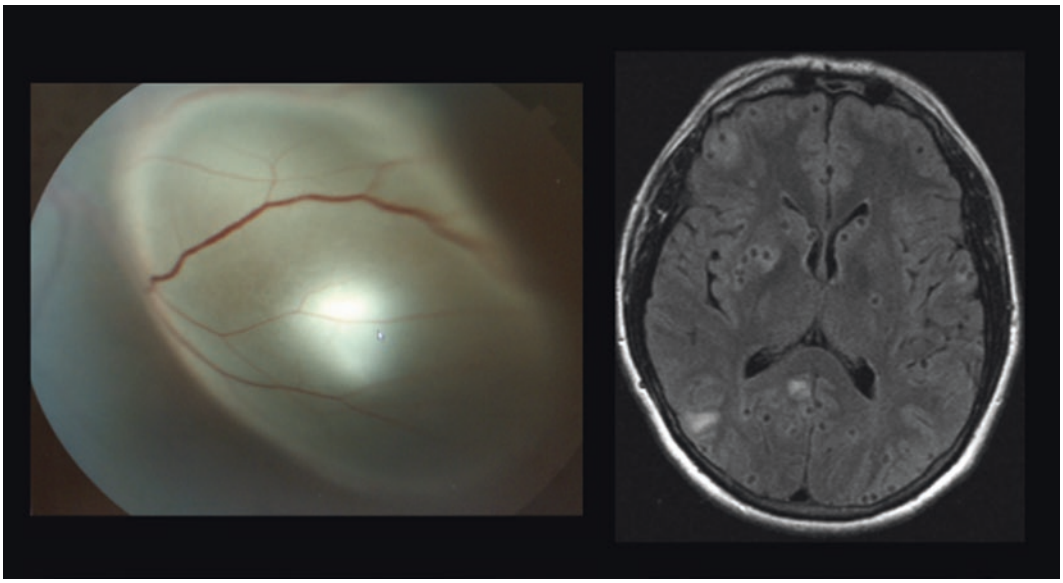

Fig. 12.6 *Left*: Fundus photo demonstrating subretinal cyst from cystercercosis with white scolex centrally. *Right*: axial FLAIR MRI sequence demonstrating multiple cystic lesions in the brain due to neurocystercercosis

throughout the body, infecting the central nervous system, eyes, and/or muscles and cysts within these tissues [47].

Epidemiology

The prevalence of cysticercosis is highest in areas with poor sanitation, where pigs roam freely and consume human feces [47]. Cysticercosis is endemic in Andean South America, Brazil, Central America and Mexico, China, the Indian subcontinent and South East Asia, and sub-Saharan Africa [47].

Systemic Manifestations

There are two clinical forms of cysticercosis. In focal cysticercosis, the parasite invades the muscles or perimuscular tissue only. The other form is systemic or central nervous system disease [47].

Cysts within the brain and spinal cord cause the most severe form of the disease, called neurocysticercosis. This may be asymptomatic, or cause seizures, headaches, confusion, difficulty with balance, cerebral edema, hydrocephalus, stroke, or death. Cysts in the muscles are usually asymptomatic, but can cause tender lumps under the skin [47].

Ophthalmic Manifestations

Intraocular cysticercosis is a manifestation of systemic disease, while orbital/adnexal cysticercosis is a manifestation of focal disease. *T. solium* reaches the eye via the posterior ciliary vessels and nerves [47].

Patients with intraocular disease may present with loss of visual acuity, scotoma, or eye pain. Many will also have coincident central nervous system disease. In orbital or adnexal disease, symptoms depend on the size and location of the cyst [46].

The most common form seen in children is orbital/adnexal cysticercosis. The most common site of cyst formation include the extraocular muscles, subconjunctival space, eyelid, optic nerve, retro-orbital space, and lacrimal gland [47] (Fig. 12.6).

Intraocular cysticercosis is characterized by cysts floating in the anterior chamber or vitreous, or posteriorly lodged in the subretinal space. Visual loss occurs if there is macular involvement. Death of the encysted parasites incites a severe inflammatory response and scarring, leading to scarring and possible visual loss [47]. Often, fundus examination is difficult due to the presence of significant vitritis and vitreous opacities. B-scan is routinely warranted and allows visualization of the cyst wall and the parasite within the cyst. Stimulation of parasite with light can elicit movement [46].

Diagnosis

Diagnosis is made by direct visualization of the cyst on tissue biopsy or inside the eye, or with cyst movement on B-scan. It can also be confirmed by serum antibodies or by parasite detection in the stool, either by direct visualization or by antigen testing [47].

Stool is not a sensitive way to diagnose cysticsercosis, so a negative result will not rule out cysticercosis infection of the eye.

Management

For orbital or adnexal disease, surgical removal of the cyst is the treatment of choice for accessible lesions. Lesions that cannot be surgically removed are treated systemically with Praziquantel (50 mg/kg/day) along with corticosteroids to reduce inflammation [47].

Antihelminthic therapy is not recommended for patients with intraocular disease, as it can precipitate severe inflammation, causing inflammatory phthisis or severe visual loss. The treatment of choice is surgical removal of the encysted parasite [47].

If patients present with intraocular and systemic disease, which is often the case, the surgical removal of the parasite should be performed before systemic treatment. Thus a thorough eye exam is recommended prior to the initiation of antihelminthic treatment in patients with neuro-cysticercosis.

Onchocerciasis (River Blindness, Filariasis)

Definition

Onchocerciasis, also known as river blindness and Robles disease, is caused by the nematode *Onchocerca volvulus*. The parasite is transmitted to humans by the bite of *Simulium exiguum,* also known as the black fly. Adult female worms are transmitted from the bite into the subcutaneous tissue, where the worm lays eggs. The eggs hatch into microfilaria [46].

Epidemiology

The World Health Organization estimates that onchocerciasis is the second leading cause of infectious blindness worldwide, with 17 million people infected, 270,000 of whom are blind and 500,000 of whom are visually impaired. 123 million people are at risk for becoming infected with the parasite [46, 49]. The disease is most prevalent in Africa, where 99 % of cases are seen and people in 28 countries are affected [50]. It is also found in Yemen and Central and South America [46].

Systemic Manifestations

Other than ocular involvement, onchocerciasis primarily affects the skin. Skin manifestations include acute and chronic papular dermatitis, scratch marks, lichenification, and pigmentary changes known as "leopard skin" [48].

Ophthalmic Manifestations

Individuals with ocular involvement will invariably have dermatologic involvement [48]. Ocular symptoms include visual impairment, including visual field loss and blindness, eye pain, irritation, and itching skin lesions [48, 49].

When deposited near the eye, the parasite migrates through the skin or bulbar conjunctiva into the cornea, anterior chamber, and iris. They enter the posterior chamber via the ciliary vessels and nerves. Dead or degenerating worms incite a severe inflammatory reaction leading to scarring and local inflammation, which can cause significant visual morbidity [46].

Ocular disease is classified into two types: savannah and rainforest. Blindness is more common in the savannah type, and is mainly caused by a punctate or sclerosing keratitis, snowflake corneal opacities, and iridocyclitis with a characteristic pear-shaped iris deformity (torpid iritis). In rainforest onchocerciasis, blindness is less common and is caused by posterior segment involvement, including peripheral chorioretinal lesions, vascular sheathing, and optic neuritis leading to optic atrophy. In addition to these ocular findings, microfilaria may be visualized in the cornea or anterior chamber on examination [46, 48].

Diagnosis

The diagnosis of onchocerciasis is confirmed by observation of live microfilaria in biopsy specimens of symptomatic skin nodules [46].

Management

Ivermectin, 150 mg/kg annually is the treatment of choice. Suramin may be used in cases that are resistant to ivermectin [46].

Phthiriasis Palpebrarum

Definition

Phithriasis palpebrarum is a rare parasitic infection of the eyelashes and eyelids caused by the pubic louse, *Phthiriasis pubis,* and its ova. Humans are the only host, and transmission is by direct human-to-human contact, although fomites, such as bedding and clothing may also play a role [51]. Because of its mode of transmission, a diagnosis of *phithriasis palpebrarum* in children should always raise concern for child abuse and involvement of child protective services may be warranted [52].

Epidemiology

Phithiriasis pubis infestation is found worldwide and occurs in all races and ethnic groups and all levels of society. Infestation of eyelashes or eyelids, however, is very rare. As noted above, when seen in children, it raises concern for sexual exposure or abuse [53].

Systemic Manifestations

Ophthalmic disease may be isolated, but individuals can also present with signs and symptoms of pubic involvement. The most common symptom is pruritis of the pubic and groin area [53].

Ophthalmic Manifestations

Presentation of ocular disease includes pruritus and irritation of the skin around the eye, including the lid margins and conjunctiva [52].

Ocular findings can include secondary blepharitis, follicular conjunctivitis, periauricular lymphadenopathy, and marginal keratitis. Examination may reveal conjunctival injection, eyelid erythema and swelling. Adult lice, nits (ova), and their excretions can be visualized at the base of the eyelashes [52].

Diagnosis

Diagnosis is based on clinical examination through observation of adult lice and nits on the eyelashes under magnification [52].

Management

There is no single treatment plan that has been determined to be optimal for the treatment of *Phithriasis palpebrarum*. Treatment should include mechanical removal of the lice and nits with jewelers forceps or plucking/trimming of the eyelashes. Additional treatment should include a topical pediculocidal agent, such as fluorescein 20 %, physostigmine, 0.25 %, mercuric oxide 1 % ophthalmic ointment and ammoniated mercury 3 % ophthalmic ointment, 1 % malathion drops or shampoo, and pilocarpine gel 4 %. Any ointment, including petroleum jelly or water-based gels, can be used to smother the lice. Treatment is recommended for 2 weeks, which corresponds to the life cycle of the louse [52]. Any items of close contact including bed sheets and clothing should be washed and dried at 50 °C or higher [52].

Viruses

Herpes Simplex Virus

Definition

Herpes simplex virus (HSV) is a double-stranded DNA virus. There are two types, HSV-1 and HSV-2. In general, infections with HSV-1 are above the waist and HSV-2 occur below the waist in sexually active individuals, however that is not an absolute and either virus can present in any location. All human herpes viruses establish latency and can reactivate. Reactivitation of HSV-1 and HSV-2 manifests as disease, typically vesicles in the oral or genital areas, or can be asymptomatic, typically shedding in the same areas. Additionally, HSV-1 and 2 can cause disseminated disease [5].

Epidemiology

HSV infections are ubiquitous with seropositivity of HSV-1 estimated to be over 25 % by the age of 7 [5] and between 50 and 90 % by adulthood [54, 55]. HSV is transmitted by direct contact from virus shed by HSV lesions or oral or genital secretions that harbor the virus. Thus, sexual abuse should be suspected in cases of HSV-2 infection in pre pubertal children.

It is estimated that 0.15 % of the US population experiences recurrent ocular infection due to the HSV virus [54]. Children have a worse visual prognosis due to corneal HSV infections than their adult counterparts due to a higher rate of late or missed diagnosis (up to 30 %) leading to more corneal scarring and amblyopia [56]. Additionally, children are more likely to have HSV recurrence, bilateral disease, and are more likely to have stromal keratitis than adults [56].

Intrauterine infections are rare, but can cause significant risk to sight due bilateral congenital cataracts, keratitis, conjunctivitis, and chorioretinitis. Neonatal infections are generally due to transmission of HSV-2 during birth and about 15–20 % of infants who have a neonatal HSV infection have some eye involvement [54].

Systemic Manifestations

Primary HSV-1 infection in an immunocompentent host is generally asymptomatic, but can sometimes cause pharyngitis, submandibular lymphadenopathy, and the classic gingivostomatitis. There is an incubation period of 2–14 days and then vesicles and fever develop. Symptoms resolve over the next 2 weeks. Recurrent HSV-1 infection is generally more mild and begins with paresthesias in the affected areas followed by vesicles and pain. It takes 3–10 days for the vesicles to crust and completely heal.

Primary HSV-2 infections incubate for about a week and are often asymptomatic. Similar to HSV-1, symptoms of a HSV-2 infection can include fever, lymphadenopathy and vesicle formation. Generally vesicles are in the genital area. Recurrent HSV-2 infections are also milder than primary infection.

Patients with neonatal HSV infection will present with symptoms between birth and 6 weeks of age. Twenty-five percent of patients with a neonatal infection have disseminated disease that can include liver, lung and central nervous system involvement. Less than half of patients with disseminated disease have only skin, eye and or mouth disease (SEM disease) and about 30 % of cases have CNS only disease [5]. Many of these patients who have disseminated HSV disease will present without the skin vesicles, making the initial diagnosis more difficult.

HSV encephalitis (HSE) can occur with primary or recurrent HSV-1 infection and can cause fever, altered mental status, and focual seizures. HSE tends to affect the temporal lobe and carries a very poor prognosis [5]. HSV can also cause meningitis or meningoencephalitis.

Ophthalmic Manifestations

Patients most commonly present with recurrent unilateral red eye associated with pain and photophobia. Patients can have a history of fever blisters/cold sores and many have a known diagnosis of HSV.

Primary eye infections usually present with a unilateral blepharoconjunctivitis with vesicles on the eyelid. Many children also have a follicular conjunctivitis. Epithelial keratitis presents in many patients with primary HSV-1 infection, often with a primary ocular infection. This is sometimes the typical dendrite, but can also be a superficial punctate keratitis, or geographic keratitis.

In recurrent ocular herpes, patient can have the epithelial keratitis as described above, but can also have a disciform keratitis, iridiocyclitis, increased IOP, or endotheliitis. Retinitis can also occur and cause acute retinal necrosis, but

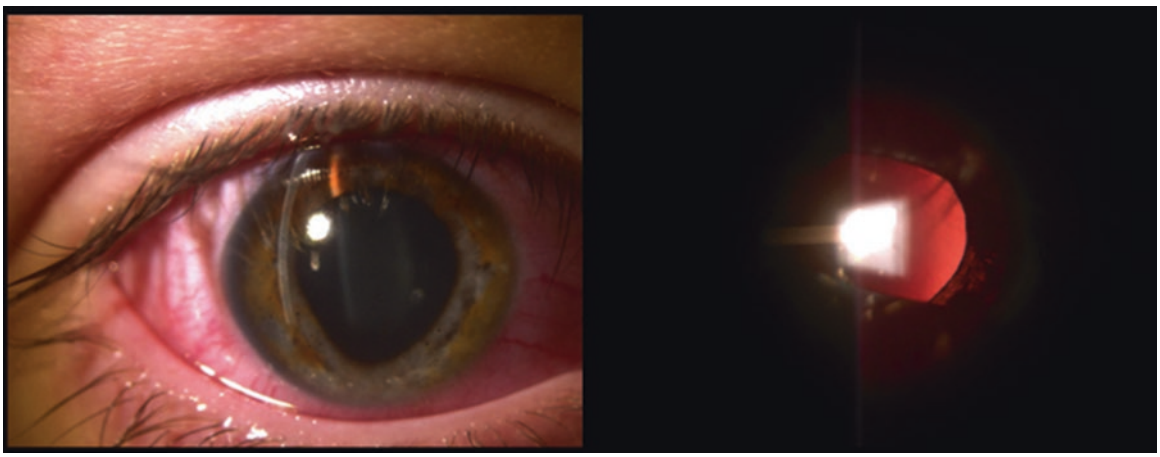

Fig. 12.7 *Left*: external photo demonstrating synechiae and pigmented keratic precipitates in patient with HSV uveitis. *Right* shows transillumination defects in same patient

this is generally rare and generally present in the immunocompromised individual.

The edges of a herpetic corneal lesion tend to have heaped up edges with swollen epithelial cells that stain with Rose Bengal or Lissamine Green. Central ulcerated portion of the HSV lesion stains with fluorescein. It is important to check for decreased corneal sensation because this can predispose the patient to secondary bacterial infections and neurotrophic ulcers.

Interstitial keratitis is an uncommon complication and can occur in the presence of iritis or glaucoma. These patients have multiple or diffuse stromal infiltrates and may not have an overlying epithelial defect [57].

The uveitis associated with HSV infection typically is associated with an increased intraocular pressure, granulomatous keratic precipitates, and iris atrophy (Fig. 12.7).

Diagnosis

Ocular HSV is usually diagnosed clinically, but cell culture, immunofluorescence, PCR, and the Tzanck smear can also be useful in the diagnosis. Serologic tests should be interpreted with caution as patients can be IgM positive with reactivitation disease and a high percentage of the population is positive serologically. Corneal or conjunctival scraping can be sent for viral culture [57].

Polymerase chain reaction (PCR) can detect HSV DNA in the CSF of neonates and older children with concerns for HSV meningoencephalitis. PCR of aqueous or vitreous fluid can be useful in certain cases.

Management

Congenital and neonatal herpes infections should be managed as an inpatient and treatment consists of intravenous acyclovir followed by long-term suppressive therapy. The duration of treatment depends on the type of infection (disseminated, skin-eye-mucous membrane, or CNS) and the long term suppressive therapy is typically a minimum of 6 months.

For eyelid and skin involvement, cool compresses as needed and topical antibiotic ointments to lesions can help with comfort. For any eyelid margin or conjunctival involvement, trifluridine or vidarabine ointment should be added.

HSV keratitis in a child can be treated with systemic acyclovir, topical trifluridine, or vidarabine ointment. Debridement of HSV epithelial lesions can promote healing, but may not be tolerated in the pediatric age group. In patients with stromal keratitis or uveitis, topical corticosteroids are indicated, but in patients with isolated epithelial disease, topical steroids are contraindicated.

Cycloplegics are indicated in patients with uveitis and can be helpful in patients with keratitis and photophobia [57].

The Herpetic Eye Disease Study Group was not designed to study the pediatric patient under 12 years old, but the results suggest that oral acyclovir helps prevent recurrent herpetic eye disease [58]. A period of acyclovir prophylaxis should be considered in children after serious disease and in recurrent disease, especially when it puts the child at risk for amblyopia or longer term vision problems.

Corneal scarring caused by herpes virus infection causes both deprivation and refractive amblyopia due to induced astigmatism, and the treatment of this amblyopia is important in restoring vision.

Varicella Zoster Virus

Definition

Varicella Zoster Virus (VZV) is also known as *Human herpes virus type 3*. Primary infection with VZV causes varicella (also known as chicken pox). After primary infection or immunization, the virus remains dormant in the dorsal root ganglion. Reactivation infection is called shingles or zoster. When the reactivation infection occurs in the V1 distribution of the trigeminal nerve, it is called herpes zoster ophthalmicus

(HZO). This usually occurs along the frontal nerve when associated with HZO [5, 59].

Epidemiology

Humans are the only host of VZV. The typical incubation period before vesicles appears 0–14 days and the host is contagious for approximately 1–2 days before the vesicular rash begins. The virus is transmitted when virus particles are aerosolized from vesicles and also by respiratory secretions. The virus does not survive on fomites.

Prior to implementation of the VZV vaccine in the United States, varicella infection occurred mostly in children under the age of 10 and often in the late winter to early spring. The incidence of VZV was so high it was almost equal to the birth rate [59]. A single vaccination was recommended in 1995 and decreased the incidence of varicella in the United States decreased by 90 % between 1995 and 2005. The recommendation for a second dose of the vaccine in 2006 has further decreased the incidence of VZV in this country [5].

The incidence of Herpes Zoster is estimated to be about 1 million cases/year in the United States. Of those cases, about 10–20 % are cases of HZO [59]. The main risk factor for HZ is increased age. While immunosuppression is a risk factor, most (92 %) of patients who get HZ are immunocompetent [60]. Treatment of HZ can reduce HZO by 50 % [59]. It is still unclear how vaccination will affect the rates of HZ over a lifetime, and many other factors will also play into HZ incidence including increasing numbers of immunocompromised individuals, people living longer, and vaccines targeted at preventing herpes zoster.

Systemic Manifestations

Primary infection with VZV causes a diffuse pruritic, vesicular rash. Systemic symptoms such as low grade fever can also occur. Occasionally patients with VZV infection can develop complications such as encephalitis, thrombocytopenia, pneumonia, hepatitis, and glomerulonephritis among others. Young children tend to be mildly symptomatic while infants, adolescents, and adults with a primary VZV infection are most affected [5].

Reactivation of VZV, also known as shingles, presents with groups of vesicles usually along 1–3 dermatomes often associated with pain and itching. In adults it is common to have a post herpetic neuralgia that can last for months [5]. The risk of post herpetic neuralgia increases with age and is rare in children.

Ophthalmic Manifestations

Patients with primary VZV infection may have mild conjunctivitis or episcleritis. Rarely, dendritic keratitis, iritis or sclerokeratitis have been reported [41].

HZO can also cause periocular pain, eye pain or foreign body sensation, blurred vision, or photophobia.

HZO presents with a varied and long list of eye problems with some patients being severely affected and others with mild or no eye involvement. The rash in HZO is similar to other cases of shingles and often starts with red painful skin progressing to macules and vesicles. This can be associated with ptosis and periorbital edema and sometimes can result in cicatricial eyelid changes as a late complication.

Cranial nerve palsies are frequent and result in double vision, though most cases are transient and self-resolving. They are thought to be secondary to associated vasculitis.

The ocular surface can be involved and patients can have scleritis, episcleritis, sclerokeratitis and even a posterior scleritis, which is quite painful. Conjunctival hyperemia and follicular reaction of the conjunctiva are relatively common.

Corneal involvement is concerning in this population. Pseudodendrites are the most classic corneal change in HZO. They are often transient, and along with punctuate epithelial keratitis usually present early in disease. Nummular anterior stromal keratitis, keratouvitis, endotheliitis, disciform stromal keratitis, interstitial keratitis, and neurotrophic keratopathy are all complications of HZO.

Posterior segment complications are rare but can be devastating. Retinal vasculitis, ischemic optic neuritis and retinal necrosis have all been reported [59]. Cases of congenital VZV, while rare, can present with cataracts, chorioretiitis, microphthalmia, or nystagmus.

Diagnosis

Herpes zoster is most usually made as a clinical diagnosis. For any diagnostic dilemmas, PCR of the fluid from a vesicle or from a scab can be diagnostic. Cell culture and direct fluorescent antibody assay (DFA) may be helpful but are less sensitive [5].

Management

In patients with a primary HZO infection, cool compresses and erythromycin ointment can help with conjunctival involvement and foreign body sensation. For patients with keratitis, topical steroid and cycloplegics can be used, but this is an uncommon presentation in patients with primary disease. Systemic antivirals are not recommended in children with primary and uncomplicated varicella infections [5, 57].

Systemic treatment with antivirals should be started in patients with HZO and in immunocompetent patients systemic steroids should also be considered. Children who are immunocompromised and or have systemic disease often need hospitalization and IV acyclovir due to poor bioavailability of oral acyclovir.

Conjunctival involvement and corneal pseudodendrites should be treated supportively with cool compresses, frequent artificial tears and lubricating ointment. Patients with immune stromal keratitis need long term steroid treatment,

tapered over months and sometimes years. Uveitis associated with VZV infection should be treated with standard topical steroids and cycloplegics with care to watch for intraocular pressure (IOP) rise and also treat ocular hypertension aggressively with aqueous suppressants. Neurotrophic keratitis is difficult to treat and long term management often includes bandage contact lenses, aggressive lubrication, tarsorrhaphy and sometimes ambiotic membrane grafting. Complications of neurotrophic cornea, specifically corneal ulcerations, need to be managed aggressively and take a long time to heal. In children, amblyopia frequently occurs secondary to these complications and also requires treatment [57].

Patients with HZ infection and eye involvement need to be followed frequently during the first week of infection to ensure that they are healing appropriately and that there is no corneal melt or secondary infection.

Measles (Rubeola)

Definition

Measles, also known as rubeola, is caused by a single-stranded RNA virus of the genus Morbillivirus in the Paramyxoviridae family [61–63]. Humans are the only natural host and transmission is via direct person-to-person contact or airborne droplets. The virus can remain infectious for up to 2 h in the air. It is considered one of the most contagious of all infectious diseases by the Center for Disease Control and Prevention (CDC) as reportedly 9 out of 10 susceptible individuals who come into contact with the virus will develop clinical symptoms [61]. Infectivity is greatest in the 3 days before appearance of the rash.

Epidemiology

In cases of congenital measles infections, a history of measles infection during pregnancy can be elicited [62, 63].

Before development of the measles vaccines over 40 years ago, the measles virus affected 95–98 % of children by age 18 years [64]. Prior to the institution of vaccination programs, approximately 48,000 people were hospitalized and 1000 people were plagued with chronic disability from measles-related acute encephalitis in the United States each year. The measles containing vaccine is administered as a combination vaccine, called the measles-mumps-rubella (MMR) vaccine which is 93 % effective in preventing measles after just one dose [61]. However, despite the existence of this vaccine, measles still remains the fifth leading cause of infectious mortality among children younger than 5 worldwide [62, 63]. The CDC estimates that 20 million people worldwide are infected with measles annually of which over 100,000 die. While still prevalent worldwide, in the year 2000, measles was declared eliminated from the United States. Still, because of high rates of worldwide travel and variable compliance with vaccination programs, measles cases and outbreaks still occur in the U.S. with numbers ranging from 37 reported cases in 2004 to 668 in 2014 [61].

Those are highest risk for severe illness and complication include children under the age of 5 years, adults over the age of 20 years, pregnant women, and immunocompromised individuals [61].

Systemic Manifestations

Measles is an acute respiratory illness characterized by a prodrome of high fever (up to 105 °F) followed by a maculopapular rash and the "three C's"; cough, coryza and conjunctivitis. The virus has an incubation time of 7–21 days, however the pathognomonic maculopapular rash typically appears 14 days after exposure [61, 64]. The rash begins on the face and neck as discrete erythematous lesions which then spreads to the trunk and lastly to the extremities. Koplik spots, bluish-white lesions on an erythematous base, can be found on the buccal mucosa, soft palate, conjunctiva, and vaginal mucosa in 60–70 % of patients with measles.

The most common complications related to measles are otitis media, bronchopneumonia, laryngotracheobronchitis (also known as "measles croup") and diarrhea. Bronchopneumonia and otitis media are theorized to be due to secondary viral or bacterial infections rather than directly related to the measles virus. Other serious complications include febrile seizures, post-infectious encephalomyelitis and acute encephalitis. One out of every 1000 people with measles will develop acute encephalitis which can unfortunately often leads to permanent neurologic complications.

A rare but serious complication, subacute sclerosing panencephalitis (SSPE) occurs in one out of every 8.5 million people infected with measles. This fatal slowly progressive demyelinating disease typically presents with behavioral and other neurologic changes 7–10 years after initial infection. It is caused by the persistence of the measles virus within the central nervous system. At this time, it is unknown what factors predispose an individual to this complication, but it is theorized that infection prior to the age of 2 years may increase risk [61, 63, 65].

Ophthalmic Manifestations

In addition to the typical systemic complaints, patients may present with non-purulent conjunctivitis or eye irritation and blurry vision [62–64].

The most common ophthalmologic complication in persons with measles is a nonpurulent, papillary conjunctivitis; reported in up to 65.6 % of patients. Koplik spots may also be present on the conjunctiva, but are rare. Keratitis has been reported to occur in as high as 57 % of people affected. Typically the corneal and conjunctival changes resolve without permanent sequelae. However, worldwide, in patients with vitamin A deficiency, the keratitis is often

more severe and can lead to blindness [62–65]. Acute acquired measles retinopathy has been described as well. This typically presents with profound vision loss, attenuated arterioles, retinal and optic nerve edema with or without macular star, and retinal hemorrhages. Electroretinogram (ERG) testing is typically extinguished during the acute phase but may return to normal with resolution of inflammation. Acquired measles retinopathy resolves over weeks to months. Most patients retain some useful vision but prognosis is still guarded [62, 63].

Ocular manifestations of congenital measles include congenital cataracts, optic nerve head drusen and bilateral pigmentary retinopathy. Congenital measles retinopathy, less common than the acquired type, typically involves pigmentary changes in both the posterior pole and peripheral retina. Other findings such as attenuated vessels, retinal edema or macular star may also be present. In contrast to acquired cases, the ERG in congenital cases is typically normal [62, 63, 66].

Diagnosis

Diagnosis was traditionally made clinically. However, Laboratory confirmation is now used for sporadic cases and outbreaks. Presence of measles specific IgM and measles RNA by PCR testing is diagnostic. Testing requires both serum samples and nasopharyngeal swabs from suspected patients and urine samples can also aid in the diagnosis [61]. Other forms of serologic testing is available including complement fixation and ELISA testing [62, 63]. Healthcare providers in the U.S. are required to report suspected cases to their local health department within 24 h [61].

Management

Treatment for measles consists of supportive care and symptomatic relief. Those who develop secondary bacterial infections or complications are treated accordingly. Vitamin A is now recommended for severe, hospitalized cases in children and is administered based on guidelines developed by the World Health Organization. Post-exposure prophylaxis (PEP) is available for any persons exposed to measles who have not previously been immunized. In such cases, the MMR vaccine should be administered within 72 h of exposure. For immunocompromised individuals including infants younger than 1 year or unimmunized pregnant women who were exposed to the virus, intramuscular or intravenous immunoglobulin can be administered within 6 days of exposure [61].

Rubella

Definition

Rubella, also known as the German Measles, is a caused by the rubella virus, an RNA virus of the *Togaviridae* family and *Rubivirus* genus which is spread by nasophayngeal secretions [63, 67]. Since advent of the vaccination against the rubella virus in 1969, cases of acute rubella infection have fallen dramatically. Acute infection during childhood often produces a mild viral illness associated with a characteristic rash. However, primary infection acquired during pregnancy can cause devastating birth defects, called Congenital Rubella Syndrome (CRS) [63, 68, 69].

Epidemiology

In the pre-vaccine era, rubella infection occurred in epidemics and was most common in young children, ages 5 to 9 years. The last pandemic of Rubella occurred between 1963 and 1965. During this pandemic, in the United States, there was an estimated 12.5 million cases of acquired Rubella, more than 13,000 fetal or infant deaths, and a reported 20,000 infants with serious rubella related congenital defects [68].

The introduction of the rubella vaccine, now administered as part of the Measles, Mumps and Rubella vaccine, has dramatically decreased rates of Congenital Rubella Syndrome (CRS) as well as acute infections in adults. Because of vaccination programs, rates of seropositivity to Rubella in the United States are >95 % in the adult population. According to the CDC, between 2005 and 2011, only 4 cases of CRS were diagnosed in the United States. However, in developing countries, some sources estimate that up to 68 % of adults are still susceptible to acute infection. Worldwide, it is estimated that over 100,000 infants are born with CRS annually [63, 68, 70].

Congenital Rubella Syndrome (CRS) occurs because the rubella virus is able to cross the placenta during gestation. The risk of developing CRS declines with advancing gestational age. For instance, infection during the first 12 weeks of gestation is associated with a 90 % chance of developing CRS and almost a 100 % chance of congenital defects, while primary infection from 18 to 24 weeks has a 25 % risk of CRS [71].

Systemic Manifestations

The most important historical finding is a history of maternal infection with rubella during pregnancy or a lack of immunity against rubella during pregnancy.

Acquired rubella infection has a usual incubation time of 15–21 days followed by the appearance of a maculopapular rash which begins on the face and head and spreads downward to the trunk and then extremities. Some patients may experience a prodromal illness several days before the appearance of the rash which may include malaise, fever, lymphadenopathy, anorexia, headache and conjunctivitis. Forchheimer's spots are small petechial lesions of the soft palate which can sometimes be seen in the prodromal phase. Prodromal symptoms are more common in adults than children. Young adults often experience arthralgia and joint swelling. Other less common findings include thrombocytopenic purpura, encephalitis, and testicular pain [63, 71].

Congenital rubella infection can affect essentially any organ system. The traditional CRS triad consists of cardiac, ocular, and hearing disorders. Some of the most common clinical sequelae that have been reported include; deafness, mental retardation, microcephaly, ocular sequelae (detailed below) and cardiovascular defects such as patent ductus arteriosus, interventricular septal defects, and pulmonic stenosis. Other reported systemic findings include intrauterine growth restriction, thrombocytopenia, hepatosplenomegaly, hypospadias, hepatitis, interstitial pneumonitis, cerebral calcifications, meningio-encephalitis, nephrosclerosis, nephrocalcinosis, bone lesions, skin lesions and dental defects. In more severe cases, CRS can cause intrauterine death [63, 68, 70]. Late sequelae of CRS include thyroid disease and significantly higher rate of diabetes mellitus than the general population [68].

Ophthalmic Manifestations

Ocular signs of acquired rubella tend to be mild. Conjunctivitis is the most common manifestation seen in approximately 70 % of cases. A central epithelial keratitis is seen in <10 % of patients and typically completely resolves within a few days. Only a few cases of acquired rubella retinitis have been reported. These cases were described as disseminated chorioretinitis with multiple bullous retinal detachments, RPE depigmentation and mild vitritis and uveitis all of which resolved with some remaining atrophic areas [63].

Ocular sequelae are considered part of the CRS triad. Nuclear cataracts, microphthalmia, glaucoma, and a pigmentary retinopathy are the most commonly described manifestations. Rubella cataracts are essentially always nuclear, either unilateral or bilateral and opaque in appearance. The fetal lens nucleus acts as a viral reservoir post-natally which may explain why the cataract progresses [63, 72]. CRS retinopathy is a non-progressive pigmented retinopathy which can involve any quadrant but characteristically involves the posterior pole and macula. The pigmentary changes described range from fine powdery deposits to discrete black patches throughout the fundus and represent areas of retinal pigment epithelium atrophy. It has previously been described as a "salt-and-pepper" retinopathy [63, 68, 72]. Visual prognosis is relatively good in these patients unless complicated by a neovascular membrane or scarring [68]. Congenital and secondary glaucoma are less frequent findings but have been reported in up to 10 % of CRS patients [63, 72].

Diagnosis

Acquired and congenital cases of rubella are often suspected clinically but require laboratory confirmation for formal diagnosis. Identification of the virus in serologic samples or increasing titers of rubella specific antibodies over time (IgM or IgG) can be used for diagnosis [63, 68]. Serologic tests include, Enzyme-linked immunosorbent assay (ELISA), Complement fixation testing (CF), Hemagglutination inhibition test (HI), fluorescence immunoassay (FIA), radioimmunoassay (RIA), latex agglutination (LA) and passive hemagglutination (PHA) [63]. PCR is the preferred test for rubella diagnosis [73]. In infants with CRS, IgM can be identified in their cord blood for up to 6–12 months after birth [70]. Amniocentesis, chorionic villus sampling (CVS) and fetal blood testing can be performed to diagnose a rubella infection during pregnancy [68].

Management

Acquired cases of rubella are treated supportively and sequelae are treated as appropriate. Systemic complications from CRS should be treated as they are identified. Since CRS cataracts are centrally located they are considered visually significant and therefore early extraction is recommended to prevent sensory deprivation, amblyopia and strabismus. If glaucoma is present it too should be appropriately addressed early. CRS retinopathy rarely requires any treatment unless complicated by a neovascular membrane [63, 68].

The immune status of all pregnant women and patients of unknown immunity should be investigated. Patients without evidence of prior immunization should be immunized immediately. The vaccine, however, is contraindicated in immunocompromised patients, pregnant women, and those who intend to become pregnant within 3 months of the immunization date. Gamma globulin administration can prevent clinical disease in unimmunized pregnant women exposed during pregnancy, however transmission to the fetus can still occur [63].

Cytomegalovirus Infection (CMV)

Definition

Cytomegalovirus (CMV) is a member of the herpes virus family *(Herpesviridae)*. It is a ubiquitous virus and its pathogenicity relies on both the mode of transmission and the immune status of the host.

Patient History Related to Eye

Patients infected congenitally with CMV are often asymptomatic. Symptomatic patients most commonly present with hearing loss and are subsequently referred for eye exam. In severe cases, patients infected with CMV in utero will have visual impairment [74] but will not have eye pain or redness or other findings that would be noted by parents.

Patients who acquire CMV and have eye symptoms may complain of decreased vision, scotoma, photopsias, floaters, and rarely eye pain [75].

Epidemiology

The two pediatric populations most commonly affected by CMV are those with congenital infection and patients who are immunocompromised. CMV is the most common congenital infection in humans and is acquired congenitally in up to 1–2 % of live births however up to 90 % of these congenital CMV cases are thought to be asymptomatic [74].

The rate of CMV viremia in patients after hematopoeietic stem cell transplants (HSCT) ranges in the literature from 18[57] to 51 %[77]. Of those who develop viremia, the rate of CMV retinitis is also variable (5–23 %) [76, 77]. In the authors' experience there has been an increase in the rate of CMV retinitis in pediatric patients who have received HSCT [78].

Pediatric patients with acquired immunodeficiency syndrome (AIDS) have a lower rate of CMV retinitis than their adult couterparts and tend to have lower CD4 counts before developing disease [79].

Ophthalmic Manifestations

During an acute infection with rubella, patients may complain of visual changes, ocular irritation, redness or hyperemia [63].

Optic atrophy, macular scarring, and cortical visual impairment are the most common eye abnormalities in patients with congenital CMV infection [74]. Patients who have asymptomatic congenital CMV infection are much less likely to have or visual problems than those who have symptomatic infections[74] Approximately 22 % of symptomatic patients with congenital CMV infection will have some degree of vision loss [74].

The retinitis in acquired CMV causes a granular appearance of the retina in mild cases and more severe forms present with retinal necrosis, hemorrhage and exudates. Rhegamatogenous retinal detachment can occur, usually when a large amount of the retina is involved. Vitreous cell may or may not be present and is usually mild.

Systemic Manifestations

Most children are asymptomatic from congenital CMV infection. The most common symptom in congenital CMV infection is hearing loss [74, 80]. Intrauterine growth retardation (IUGR), hepatomegaly, and microcephaly are seen in more severe congenital CMV infections [5].

Immunocompetent patients who acquire CMV generally have a mild illness with fever and mild hepatitis. Patients who are immunocompromised, however, can have primary or reactivation disease that is systemic or organ-specific including pneumonia, colitis, hepatitis, and encephalitis [5].

Diagnosis

Cytomegalovirus can be detected in the cell culture in a variety of body fluids. Additionally PCR of viral DNA of white blood cells can be used to diagnose CMV. CMV retinitis is often a presumed, or clinical diagnosis in the right clinical setting. A positive PCR of aqueous or vitreous fluid can help aid in the diagnosis but is not necessary [5].

Management

Congenital CMV is typically not treated unless the baby is symptomatic or there is concern for central nervous system involvement. In these cases, treatment with 6 months of oral valganciclovir is thought to help aid in the protection of the nervous system and prevention of continued hearing loss [81].

The systemic antivirals ganciclovir, foscarnet and cidofovir can all be used alone or together to treat systemic CMV infection. CMV can become resistant to antivirals, particularly in immunocompromised patients, and combination or changing therapies may be required to effectively treat the retititis.

In cases of CMV retinitis that threatens the fovea, optic nerve, or is progressive despite systemic treatment, intravitreal injections of ganciclovir and/or foscarnet are recommended.

Relapse of CMV is common and the ultimate treatment is to reestablish natural immunity.

Epstein-Barr Virus Infections (Infectious Mononucleosis)

Definition

Epstein-Barr virus (EBV), also known as *human herpes virus 4* (HHV-4), is a DNA virus of the herpes virus family. It is a ubiquitous virus with >90 % of the adult population having serologic evidence of previous infection [82, 83]. It is transmitted via direct contact with bodily fluids, most often saliva [84].

Epidemiology

The EB virus can be serologically identified in >90 % of the adult population. Infection is generally subclinical in children and infants. However, when exposure is delayed and primary infection occurs in adulthood, it manifests as Infectious Mononucleosis (IM) [82, 83].

EBV has been linked to Burkitt Lymphoma, nasopharyngeal carcinoma, and thyroid carcinoma as well as other lymphoproliferative disorders [85]. Burkitt Lymphoma is endemic to certain equatorial regions of Africa with a reported incidence of 100 cases per million children in these regions [86]. A possible association with Sjogren's syndrome has also been proposed [85, 87].

Systemic Manifestations

Primary infection during infancy or childhood is traditionally subclinical. Primary infection during adolescence or adulthood manifests as infectious mononucleosis (IM). IM is

characterized by a triad of pharyngitis, lymphadenopathy, and fever. Associated symptoms may include fatigue, malaise, anorexia, nausea or vomiting, myalgia, arthralgia, headache, chills. Splenomegaly is found in up to 50 % of patients. After initial infection, the virus remains latent in the body [82–85].

Ophthalmic Manifestations

Reported cases of systemic EBV related ocular findings include all segments of the eye and therefore initial presenting complaints vary greatly. Ophthalmic symptoms may include but are not limited to visual impairment, ocular irritation, orbital and adnexal masses, photophobia and pain [85].

Ocular manifestations of EBV divided based on the segment affected, include:

- External and adnexal disease: periocular edema, dacryoadenitis, eyelid masses, and Parinaud's oculoglandular syndrome. Presence of a granulomatous conjunctival mass in addition to an enlarged pre-auricular lymph node is diagnostic of Parinaud's Oculoglandular syndrome [85, 87].
- Anterior segment: follicular conjunctivitis, stromal or epithelial keratitis, episcleritis, scleritis, conjunctival lesions, dry eye syndrome and bilateral anterior uveitis [85, 87].
- Posterior segment: macular edema, papillitis, retinal hemorrhages, vitritis, retinitis, choroiditis, progressive subretinal fibrosis and secondary choroidal neovascularization. Choroidal lesions appear as gray to yellow infiltrates that later become punched out areas of pigment epithelial scarring. Vitreous inflammation is commonly present with retinal or choroidal involvement [85].
- Neurologic: optic nerve edema, optic neuritis, bilateral ptosis, ophthalmoplegia, and cranial nerve palsies [85, 87]. Cranial nerve III, IV, VI, and VII palsies have also been reported.

Of those reported, the most common manifestation is a mild, follicular conjunctivitis which occurs early in the course of the primary infection [85, 87]. Though rare, congenital EBV has been associated with congenital cataracts [66].

Diagnosis

Epstein-Barr virus and Infectious Mononucleosis are both typically diagnosed clinically. A variety of serologic tests exist which detect antibodies against EBV specific antigens; Viral Capsid Antigen (VCA), Early Antigen (EA) and EBV Nuclear Antigen (EBNA). Both anti-VCA IgM and IgG can be identified and are used to delineate active versus past infection. Anti-Early Antigen IgG, if present, is traditionally a sign of active infection. The EBNA antibody is not present until 2–4 months after symptom onset and is therefore a marker of past infection [82, 84]. The Monospot test or Heterophile Antibody Test has both high false positive and false negative rates. While previously traditionally used, according to the CDC, this test should no longer be routinely used for diagnosis [84].

Management

Acute EBV infection and infectious mononucleosis (IM) are usually self-limited infections. Therefore, treatment consists of supportive therapy and symptomatic relief. Those with spleen or liver involvement of IM are advised to avoid contact sports and strenuous activity [85]. The utility of antivirals have not been established [87]. Treatment of the various ocular manifestations varies based on presentation [82–85].

Molluscum Contagiosum

Definition

Molluscum contagiosum is considered a benign, self-limited skin eruption caused by a large double-stranded DNA virus of the *Poxvirus* family and *Molluscipox* genus. It most commonly affects children and is transmitted via direct physical contact with a lesion or via fomites. There are also reports of sexual transmission, which more commonly affects young adults [88, 89].

Epidemiology

Molluscum contagiousum most commonly affects children and is spread via direct contact with lesions. More recently, there have been increasing reports of sexually transmitted cases in young adults affecting the genital region [88, 90]. Anecdotal reports have suggested transmission via public swimming pools or saunas, but these reports have been unable to be substantiated [91]. Typical or atypical lesions are also seen in immunocompromised individuals and when present tend to be more severe, more widespread and less responsive to traditional treatment [88, 90, 92].

Systemic Manifestations

Molluscum lesions are found on the skin or mucous membranes. They are traditionally small, 2–5 mm in diameter, firm, pearly-white or skin colored papules with central umbilication [88]. They are found in clusters primarily on the face, trunk, limbs and genitalia and are usually asymptomatic. Occasionally, a patient will complain of itching around the site of a lesion [88–90].

In immunocompromised patients, the presentation may be more severe and widespread. In such cases atypical appearing lesions are common. Rather than clusters of individual lesions, immunocompromised patients often present with larger, confluent, coalescing plaques. Further, lesions in HIV patients are more likely to recur after treatment than in immunocompetnant individuals. Prior to the advent of

HAART therapy, 5–18 % of HIV positive patients suffered from severe molluscum infections. Widespread molluscum infection is now often considered a marker for immunodeficiency [88, 92].

Ophthalmic Manifestations

Ocular molluscum lesions most often occur on the eyelids, though conjunctival lesions have been reported [90]. Other ocular manifestations include a chronic follicular conjunctivitis and keratitis. The conjunctivitis can be accompanied by a punctuate keratopathy and epithelial or subepithelial corneal infiltrates as well. It is hypothesized that the follicular reaction is secondary to either a hypersensitivity or toxic reaction to virus particles shedding into the tear film from the associated lesion. This conjunctival reaction can appear prior to identification of a lid lesion and subsequently is often initially misdiagnosed and inadequately treated [89–91].

Diagnosis

Diagnosis is primarily clinical, based on history and characteristic appearance of lesions. In some cases, histopathological diagnosis is warranted and can be obtained via biopsy or excision [90]. In such cases histopathologic examination reveals large, eosinophilic, cytoplasmic inclusion bodies, called Molluscum Bodies or Henderson-Patterson bodies [93]. These inclusion bodies may also be observed within the material at the lesion's core if aspirated [90, 91, 93].

Management

Skin and eyelid lesions are generally self-limited. However, various modalities do exist to treat these lesions. Podophyllotoxin 0.5 %, Imiquimod 5 % cream, and cryotherapy have all been used with relative success. Curettage and pulsed dye and light emitting lasers have been used on non-genital lesion with varying degrees of success and there is no strong data to support their use. Other topical modalities, such as silver nitrate, salicylic acid and benzoyl peroxide have been described, but again there is little published data to support their use and such treatments are often irritating to surrounding skin [88].

Conjunctivitis is treated by excision of the causative lesion which results in complete resolution of symptoms as well as the follicular reaction within weeks of excision [89, 90]. Patients should be warned of the risk of direct spread to others as well as auto-inoculation to prevent spread of the lesions to different areas of the body [88].

Human Papilloma Virus (HPV)

Definition

Human Papilloma virus (HPV) is a DNA virus of the papillomavirus family. The virus infects epithelial cells in either the skin or mucous membranes. It is transmitted by contact, sexual contact, autoinoculation, or vertically during birth. There are over 150 known genotypes of the virus and each have different clinical associations ranging from benign lesions such as papillomas or warts to cancerous lesions [94, 95].

Epidemiology

The Centers for Disease Control and Prevention (CDC) estimate that 14 million people become infected with HPV annually and that HPV currently infects approximately 79 million Americans. According to the CDC approximately 360,000 people will obtain genital warts and 11,000 women will get cervical cancer in the United States annually. Nearly all cases of cervical cancer are associated with HPV infection [98]. Two FDA-approved HPV vaccinations now exist; the quadrivalent vaccination which targets strains 6, 11, 16, and 18, and the bivalent vaccination which targets subtypes 16 and 18. While early studies show excellent efficacy in preventing precancerous lesions in certain groups of women, controversy still exists over the high cost, the unknown duration of protection, as well as certain social implications surrounding vaccinating women at a young age [99–101].

Systemic Manifestations

HPV infects the skin, genital and oral mucosa. Specific subtypes vary in their carcinogenic potential. Low-risk subtypes are often associated with benign warts and papillomas while high-risk subtypes have been linked to cervical intraepithelial neoplasia which can lead to cervical cancer [94, 96, 99]. Twelve "high-risk" subtypes have been associated with cervical cancer thus far with just eight of them accounting for 95 % of all cervical cancers [95, 99]. The two most commonly associated subtypes are subtypes 16 and 18 [94, 95]. Both squamous cell carcinoma and adenocarcinoma of the cervix can arise from an HPV infection [99]. These "high risk" subtypes have also been linked to anal, vaginal, vulvar and penile neoplasia and neoplasias of the head and neck. Cutaneous HPV subtypes have been associated with actinic keratosis and squamous cell carcinoma of the skin, but may be less associated with basal cell carcinoma than previously thought [95].

The "low-risk" subtypes, namely 6 and 11, are associated with anogenital warts, also known as condyloma acuminata and ocular surface squamous neoplasia [96, 99]. Fortunately, infections with these subtypes are often self-limited and resolve without serious complications [99].

Ophthalmic Manifestations

Patients may report a history of a progressively enlarging eyelid or conjunctival lesion. It is important in such cases to ask about previous efforts to remove such lesions as well as episodes of recurrence. Conversely, patients may offer no history as ocular lesions secondary to HPV are often asymptomatic and found incidentally on exam [94, 96]. Rarely, in the case of a papilloma affecting the lacrimal gland, a history of unilateral epiphora, may be elicited [97].

With an incidence of 0.02–3.5 per 100,000, ocular surface squamous neoplasia (OSSN) is a spectrum of ocular surface lesions which range from mild dysplasia to squamous cell carcinoma of the conjunctiva [94]. It may appear as a focal nodule or atypical area of conjunctiva and can be associated with adjacent dilated blood vessels. These lesions have been linked to UV radiation exposure as well as HPV infection, though the reported degree of association varies. Therefore, the prevalent theory at this time is that HPV infection is one of several factors which may contribute to the development of OSSN but is unlikely the sole cause [94]. Squamous cell carcinoma of the conjunctiva can invade locally either intra-ocularly or intra-orbitally. It rarely metastasizes, but when it does, spreads first to the pre-auricular and submandibular lymph nodes [97].

HPV subtypes 6 and 11 are most commonly associated with conjunctival papillomas, though as a study published in 2010 reported, subtypes 16, 33 and 45 have also been identified [96, 102]. Papillomas may present as either exophytic, mixed, or inverted lesions, of which the exophytic subtype is the most common. They are most commonly seen in men and among people aged 20–39 and are traditionally found on the bulbar conjunctiva, by the caruncle, or, less often, at the limbus [102, 103]. Rarely they can affect the lacrimal drainage system and cause nasolacrimal duct obstruction [97].

Pterygia have also been postulated to be associated with HPV infections, though published viral detection rates in pterygia range from 0 to 100 % [94].

In one study in 83 cases of unilateral retinoblastomas (Rb) in an Asian Indian population, HPV was detected in 24 % of cases, 70 % of which contained "high-risk" subtype 16. However, the association between Rb and HPV needs to be further elucidated as multiple other small studies on this subject had contradictory reports and HPV identification rates varied greatly based on geographic population of the study [104].

Diagnosis

Polymerase Chain Reaction (PCR) and DNA sequencing are reliable for detection of HPV in tissues samples [96, 99]. Use of impression cytology pre-operatively for diagnosis of conjunctival intra-epithelial neoplasia (CIN) has been reported but it's use is limited [94]. Diagnosis of conjunctival papilloma, pterygia, and OSSN is made primarily by clinical exam and excisional biopsy when indicated.

Management

Management of a conjunctival papilloma includes observation, as some reports describe spontaneous regression of lesions, or surgical resection, usually with cryotherapy if indicated. Unfortunately, there is a high rate of recurrence of these lesions. Systemic and topical interferon therapy have been used as adjunctive therapy in cases of recurrent or multiple lesions though these each have their own associated side effects [96]. Mitomycin C, Oral Cimetidine, and Carbon Dioxide Laser have also been used with varying success in cases of recurrent or recalcitrant papillomas [105–107].

In cases of conjunctival intraepithelial neoplasia and squamous cell carcinoma of the conjunctiva, surgical excision with clear margins in addition to local cryotherapy is traditionally employed. Other therapies such as topical chemotherapy (i.e. Mitomycin-C or local interferon therapy) and irradiation have been investigated. Recurrence rates vary based on tumor size and invasiveness as well as treatment modalities and range from 17 to 41 % [108, 109].

West Nile Virus

Definition

West Nile virus (WNV) is a single-stranded, enveloped RNA arbovirus in the genus *Flavivirus* It is a member of the Japanese encephalitis virus serocomplex. The virus is transmitted to humans through the bite of the *Culex* mosquito, which acquires the virus by feeding on infected birds. Human-to-human transmission through mosquito bites does not occur. However, there have been reported cases of transmission through blood transfusion, organ transplantation, and transplacental transmission [110].

Epidemiology

There are 2 distinct lineages of the virus with differing distribution. Lineage 1 has a global distribution and is found in North America, Eastern Europe, the Middle East, West Africa, and Australia. Lineage 2 is endemic in Africa [110]. In 2014, WNV infection was reported in a total of 47 states and the District of Columbia with 2122 total cases. The largest number of cases and deaths in 2014 were in the state of California [111]. West Nile virus infection is seasonal and corresponds to mosquito season, with more than 85 % of cases being reported in August and September. Illness has been reported in the U.S. between May and December [110].

Systemic Manifestations

WNV has three clinical categorizations: asymptomatic, West Nile fever, and West Nile meningoencephalitis. Most infected individuals are asymptomatic. The symptoms of West Nile fever include sudden onset high-grade fever, headache, myalgias, and gastrointestinal symptoms. The acute illness is self-limiting and lasts less than 1 week. Neurologic disease may present as an aseptic meningitis, encephalitis, meningoencephalitis, myelitis, polyradiculitis, or optic neuritis. WNV may also affect other organs in the body as well, which can manifests as hepatitis, pancreatitis, or myocarditis [110].

Ophthalmic Manifestations

Patients may present with subjective complaints of decreased vision, floaters, photophobia, or eye pain. Reported visual acuities range from 20/25 to hand motion. Symptoms may be bilateral or unilateral [110].

The most common ophthalmic manifestation of WNV is chorioretinitis, with chorioretinal lesions in either a scattered or linear organization. The lesions appear deep, flat, yellow-white in color, may vary in size, and can become pigmented. The chorioretinits may have an associated iritis, vitritis, and intraretinal hemorrhage. Patients may also have iritis or vitritis in the absence of chorioretinitis. Another, more rare, ocular manifestation is an occlusive, hemorrhagic retinal vasculitis. There has also been one reported case of congenital chorioretinal scarring in an infant born to a mother diagnosed with WNV meningoencephalitis during her pregnancy.

As noted above, optic neuritis may be seen in association with WNV meningoencephalitis [110].

Diagnosis

ELISA to detect IgM in serum of CSF is the most commonly used diagnostic method for acute WNV infection [110].

Management

There is no proven treatment for WNV infection. Treatment is supportive. Intraocular inflammation may be treated with topical corticosteroids [110]. Ocular findings tend to be self-limited, and most patients have improvement in vision and reduced inflammation over a course of a few months [112].

Zika Virus

Definition

The Zika virus is a flavivirus related to Dengue and yellow fevers. It is transmitted mainly by infected *Aedes* mosquitoes [113]. Inter-human transmission has been described through sexual intercourse, perinatal, and through breast milk [114].

History Related to Eye Findings

Patients with primary infection may complain of symptoms commonly associated with conjunctivitis, including redness, tearing, discharge, itching/burning, blurred vision, or sensitivity to light. Mothers of infants with congenital infection may be asymptomatic or describe a self-limited illness in the first or second trimester, as described below [114].

Epidemiology

Zika virus was first isolated in humans in Uganda and Tanzania in 1952, after which few sporadic cases were reported in several countries in Africa and Asia. Reported outbreaks have occurred in Yap, Micronesia in 2007 and in French Polynesia in 2013, which spread to other Pacific islands. Circulation of Zika in the Americas was first confirmed on Easter Island, Chile in 2014. Since April 2015, an epidemic outbreak has been occurring in Brazil and has been transmitted to 27 other countries in the Americas. It is estimated that between 440,000 and 1,300,000 cases of Zika occurred in Brazil in 2015 [115]. As of April 2017, 5264 cases have been reported in the continental United States: 4963 cases in travelers from affected area, 224 cases through presumed local mosquito-borne transmission in Florida and Texas, and 77 through other routes (sexual transmission, congenital infection, laboratory transmission, and unknown) [116].

Systemic Manifestations

An estimated 80 % of people with a primary Zika infection are asymptomatic [114]. Symptomatic patients manifest with a self-limited, Dengue-like, illness characterized by low-grade fever, xanthema, conjunctivitis, and arthralgia. The rate of Guillain-Barre syndrome has been reported to increase during outbreaks [113].

Congenital infection in the first or second trimester is associated with microcephaly and central nervous system abnormalities in infants [113].

Ophthalmic Manifestations

As described above, individuals with primary infection may present with a self-limited conjunctivitis. Reported ophthalmic findings in infants with presumed congenital infection include pigmentary maculopathy, torpedo and torpedo-like maculopathy, chorioretinal atrophy, abnormal retinal vasculature, optic nerve abnormalities, iris coloboma, and lens subluxation [113].

Diagnosis

The only method of confirming infection with Zika virus is through polymerase-chain reaction (PCR) in the first days of infection. PCR does not confirm congenital infection in infants. Zika-related microcephaly is diagnosed clinically [114].

Management

There is no specific medicine or vaccine for Zika virus. Treatment is symptomatic [116].

Fungal

Coccidioidomycosis

Definition

Coccidioidomycosis, also known as Valley Fever, is a systemic fungal disease caused by two species of fungi, *Coccidioides immitis* (California species) and *Coccidioides*

posadasii (non-California species). Infection is acquired through inhalation of fungus arthroconidia in endemic areas [117].

Epidemiology

Coccidiodes is endemic in Nevada, Utah, Arizona, New Mexico, Texas, and California with the highest prevalence in Arizona. The fungus is also found in northern Mexico. Dust storms in dry, endemic regions can facilitate fungal infection in humans. Approximately 150,000 cases are reported yearly in the United States. Filipinos, African Americans, and Hispanics are more susceptible to acquiring severe or disseminated infections [117].

Systemic Manifestations

Coccidioidomycosis infection is classified in three ways: primary pulmonary, chronic pulmonary, and disseminated infection. The fungus most commonly affects the respiratory system and lungs. Sixty percent of infected individuals are asymptomatic, while the remaining 40 % will have a flu-like illness. Most people recover within 2–3 weeks, but in severe infections, patients may manifest with military lung lesions, pneumonia, hilar adenopathy, and pleural effusion, with some of these changes becoming progressive or chronic [117]. Erythema nodosum is seen in 5–10 % of females and 25 % of males with primary lung disease [118].

Disseminated disease is most often seen in immunocompromised individuals and can involve many organs including the skin, lymph nodes, spleen, liver, kidneys, bones, joints, meninges, and central nervous system. Meningeal and brain involvement is the most life-threatening [117].

Ophthalmic Manifestations

Ocular symptoms are nonspecific, ranging from no visual complaints to sudden visual loss, blurry vision, eye pain, photophobia, redness, and foreign body sensation [118].

Ocular involvement is rare, and is mainly occurs in disseminated coccidioidomycosis but can also be seen in the other forms of the disease [118].

Anterior segment findings include conjunctivitis with phlyctenules, keratoconjunctivitis, episcleritis, or scleritis, and may occur with primary pulmonary infections. These manifestations are thought to be due to a hypersensitivity response to coccidioidal antigens and resolve with time [118].

Intraocular disease may manifest as a granulomatous iridocyclitis or anterior uveitis, choroiditis, chorioretinitis, and rarely endophthalmitis. Posterior segment involvement is characterized by multiple, discrete, yellow-white fundus lesions <1 disk diameter in size. Intraocular disease is most commonly associated with disseminated coccidioidomycosis [118].

Diagnosis

Serologic testing for IgG or IgM antibodies is used to confirm the diagnosis. Sputum or tissue culture or tissue biopsy are other diagnostic options [119].

Tissue biopsy may reveal coccidioidal granulomas, which often contained double-walled spherules with endospores that can be seen on tissue pathology with H&E or periodic acid Schiff (PAS) stains [117].

Management

As noted above, most cases of primary disease will resolve spontaneously over time. The Infectious Disease Society of America recommends that antifungal treatment is warranted for patients who are immunosuppressed, have diabetes, cardiopulmonary disease, are pregnant, are Filipino or African American, or have severe illness. Extrapulmonary disease also warrants treatment. The initial treatment of choice for non-meningeal disease is an oral azole, such as ketoconazole, fluconazole, or itracanazole. Amphotericin B is an alternative therapy used in cases with rapidly progressive disease or infections in critical areas such as the spine [120].

Cryptococcosis

Definition

Cryptococcosis is a systemic fungal infection caused by the encaspsulated yeast *Cryptococcus neoformans.* The fungus lives in pigeon and bird droppings, as well as the fruit and bark of various trees. Infections in humans occur mainly through inhalation, and rarely through skin contact or ingestions [121].

Epidemiology

Cryptocooccus neoformans has a universal geographic distribution with most clinical cases occurring in the Americas or Africa. Clinically-significant infection was very rare until the onset of the AIDS pandemic. Since then 90 % of cases have been associated with AIDS, but disease is also seen in individuals with other immunocompromised states [121].

Systemic Manifestations

The initial and primary site of infection is the lung, which usually is asymptomatic or a mild illness that is self-limited. Chronic lung disease can manifest similar to tuberculosis and lung cancer with weight loss, fever, anorexia, fatigue, cough, mucous or mucopurulent sputum, hemoptysis, dyspnea, and pleural pain [121].

Primary skin infection appears as a tubercle, nodule, or abscess at the primary site of inoculation and rarely with satellite lymphangitis and lymphadenopathy. In disseminated disease, skin lesions appear as painless, ulcerative papules [121].

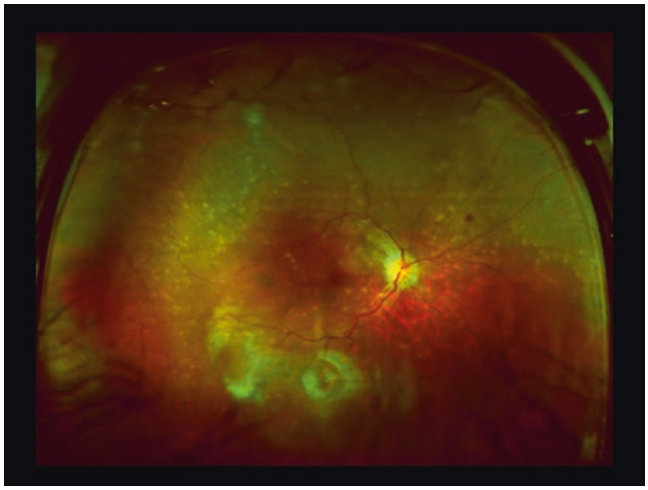

Fig. 12.8 Multifocal choroiditis in a patient with Cryptococcus (photo courtesy of Scott Oliver, MD)

Disseminated cryptococcosis presents as a severe, multi-organ disease in severely immunocompromised patients with HIV and a CD4 count of <100. Systemic signs and symptoms include fever, fatigue, weight loss, anemia, lymphadenopathy, and hepatosplenomegaly [121].

CNS cryptococcocis can occur in HIV positive or negative individuals. Those that are HIV negative may manifest with a subacute or chronic meningoencephalitis that particularly affects the basal ganglia, a mass occupying lesion, or a meningomyeloradiculitis. Immunocompromised individuals, particularly those with AIDS, will have a more acute meningoencephalitis. CNS cryptococcosis has a guarded prognosis, and without treatment is fatal [121].

Ophthalmic Manifestations

Ocular symptoms are nonspecific and may include partial or complete loss of vision, eye pain, eye redness, or photophobia.

Approximately one-third of individuals with CNS cryptococcosis will have ocular abnormalities, most commonly papilledema from elevated intracranial pressure, visual loss caused by optic atrophy, and oculomotor nerve palsy. Optic atrophy caused by intracranial hypertension, and less commonly by optic neuritis from fungal invasion of the nerve, can also occur [121].

Ocular involvement may also manifest as conjunctivitis, iritis, multi-focal choroiditis (Fig. 12.8) or chorioretinitis, or endophthalmitis [122]. The most frequent intraocular findings is multifocal chorioretinitis with solitary or multiple discrete yellow-white lesions in various sizes on fundus exam. Associated findings may include vitritis, vascular sheathing, and exudative retinal detachments [18].

Diagnosis

Diagnosis is made by observation of the encapsulated yeast via microscopy, isolation of the fungus by culture, or by demonstration of the capsular antigen in serum or CSF by latex-particle agglutination. Observation via microscopy is performed using diluted India-ink staining or phase-contrast microscopy [121].

Management

Ocular disease is treated in the same manner as CNS disease. The treatment of choice is intravenous amphotericin B and 5-fluorocytosine orally. In AIDS patients, this should be followed by 6–8 weeks of oral fluconazole. Secondary prophylaxis for AIDS patients includes oral fluconazole, oral itracanazole, or amphotericin. Secondary prophylaxis can be discontinued in AIDS patients with HAART therapy with two CD4+ cell counts of >150 in a 3-month period [121].

Histoplasmosis or POHS (Presumed Ocular Histoplasmosis Syndrome)

Definition

Histoplasmosis is a fungal infection caused by *Histoplasma capsulatum,* a dimorphic, encapsulated fungus [123]. The fungus thrives in areas contaminated with bird or bat droppings, and infection is acquired by humans through inhalation of microconidia [124].

Epidemiology

Histoplasmosis is endemenic in North, Central, and South America, as well as Europe and Africa [124]. In the United States, it is endemic in the Ohio and Mississippi river valleys, also known as the "Histo Belt."[123]. It is the most prevalent endemic fungal infection in North America [124]. Approximately 200,000–500,000 new cases occur annually in endemic areas. Exposure is common, however only ~4 % of those exposed develop ocular disease [123]. Activities that put people at risk for high inoculum exposure include cleaning chicken coupes, cleaning attics and barns, caving, construction, and other soil-disrupting activities [124].

Systemic Manifestations

The vast majority of individuals exposed to histoplasmosis are asymptomatic or minimally symptomatic and do not seek medical attention [124]. Clinically symptomatic disease is usually a self-limited flu-like illness with respiratory symptoms. However, the course and severity of the disease depends on the number of inhaled spores and the individual's immune status [123]. Clinical disease that may require anti-fungal treatment is classified into acute pulmonary histoplasmosis,

chronic-cavitary pulmonary histoplasmosis, progressive disseminated histoplasmosis and mediastinal lymphadentitis. Other disease entities include pulmonary nodules, mediastinal granuloma, mediastinal fibrosis, bronchiolithiasis, and inflammatory pericarditis, arthritis, and erythema nodosum [124].

Ophthalmic Manifestations

Patients with presumed ocular histoplasmosis may be asymptomatic or can present with acute or chronic painless, progressive blurring of central vision with metamorphopsia [123].

Ocular histoplasmosis is also referred to as Presumed Ocular Histoplasmosis Syndrome. The classic manifestation of POHS includes discrete, atrophic choroidal scars or "punched-out" lesions, peripapillary atrophy, and the absence of vitritis or anterior chamber inflammation. About 5 % will also have linear atrophic scars in the mid-periphery. The lesions are thought to be caused by disseminated *Histoplasma* that had reached the choroidal circulation leading to a subclinical choroiditis. Less than 5 % of patients with POHS will develop choroidal neovascular membranes (CNVM) from the scarring that can cause foveal compromise and severe visual decline. Smokers are at about a three times increased risk of developing CNVM from POHS [123].

Diagnosis

Diagnosis of POHS is mainly based on clinical exam findings. Antigen or antibody detection in serum or urine can aid in diagnosis [125].

Management

Treatment of ocular disease is directed toward management of CNVM. No therapy is known to reduce the risk of development of CNVM and anti-fungal do not play a role in treatment. The current standard of treatment involves intravitreal injection with anti-vascular endothelial growth factor therapy or photodynamic therapy [123].

Endogenous Fungal Endophthalmitis (Aspergillosis and Candidiasis)

Definition

Fungal endophthalmitis is infection of the ocular cavity and adjacent structures caused by fungi. We have already discussed a few causes of fungal endophthalmitis, including crytococcus and coccidiodes. Endogenous fungal endophthalmitis occurs in patients with hematologic dissemination of a fungal infection, i.e. fungemia. This section will focus on opportunistic endogenous fungal endophthalmitis caused by *Candida* species and *Aspergillus* species, although other fungi can cause same disease entity [126].

Epidemiology

Endogenous fungal endophthalmitis is very rare. Its risk factors are the same as those for fungemia and include the use of broad-spectrum antibiotics, steroids, parenteral nutrition, central venous catheters, diabetes, cytotoxic therapies, suppressive infections, and intravenous drug users. The most common causes of endogenous fungal endophthalmitis include *Candida albicans* and other *Candida* species, followed by *Aspergillus* [126].

Systemic Manifestations

As noted above, patients with endogenous fungal endophthalmitis will likely also have fungemia. Candidal fungemia is the most common cause of nosocomial fungal infections worldwide. Endophthalmitis caused by *Aspergillus* is seen in patients with pulmonary aspergillosis as well as in immunocompromised patients. Immunosupressed individuals can develop endophthalmitis from *Aspergillus* even with negative blood cultures [126].

Ophthalmic Manifestations

Patients with endogenous fungal endophthalmitis may be asymptomatic or may present with visual loss and eye pain [126, 127].

Ophthalmic manifestations involves the development of yellow-white circumscribed lesions that can be focal, diffuse, or disseminated (panophthalmitis). Patients may also develop necrosis with retinal detachments, particularly in *Aspergillus* endophthalmitis [126].

Diagnosis

Collection of vitreous humor via a vitreous tap is the most reliable method of diagnosis fungal endophthalmitis and is considered more valuable than collected aqueous humor by anterior chamber paracentesis. Vitreous and aqueous humor can be prepared on a wet mount with 10 % potassium hydroxide to visualize fungal pathogens. In candida albicans endophthalmitis, budding yeasts will be seen. Dichotomous branched hyaline septated hyphae are found in aspirates of those with *Aspergillus* endophthalmitis. Gram stain of aspirated fluid can also allow visualization of fungal elements. Definitive diagnosis is made by culture of vitreous or aqueous fluid, which should be plated on blood, chocolate, and Sabaroud agar plates and inoculated in thioglycolate broth [126]. PCR testing can also be performed on vitreous or aqueous fluid and is a more rapid method of confirmed the diagnosis compared to culture [127].

Management

The treatment of choice for fungal endophthalmitis is intravitreal injection of 5–10 micrograms of amphotericin B, without or without vitrectomy. However, amphotericin B is known to have significant potential retinal toxicity and

should be injected with caution [126]. Intraocular steroids may also be considered to help reduce inflammation [126, 127]. Systemic therapy should be administered to treat fungemia and systemic infection. Polyene and azole antifungal agents are commonly used [127].

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