Abstract

Neonatal Infections are commonly acquired in utero or during the birthing process. This ultimately can increase neonatal morbidity and mortality of the neonate, as well as having the potential of transitioning to their childhood and adult lives. TORCH syndrome is a unique acronym for a list of common infections that a neonate can acquire. This acronym was originally defined as a group of five infections that presented similarly, including a rash and ocular findings. TORCH infections comprise the following: Toxoplasmosis, Other (syphilis and HIV), Rubella, Cytomegalovirus, and Herpes simplex virus. Clinicians must always be aware of the most salient features of these TORCH infections in order to establish a timely diagnosis and management plan. Unfortunately in utero, there are limited treatment options for some of these infections; however, a diagnosis will give the physician and the patient a plan of action. Some of the neonatal features involved consist of hydropsfetalis, microcephaly, hearing loss, cataracts, seizures, heart disease, hepatosplenomegaly, jaundice, and/or rash. This chapter highlights the most important clinical features associated with TORCH infections, as well as an understanding of the transmission, clinical manifestations, diagnosis, and treatment of these infections.

Keywords: Cytomegalovirus (CMV); Herpes simplex virus (HSV); Intrauterine infection; Neonatal infection; Pregnancy; Rubella; TORCH; Toxoplasmosis

Introduction

TORCH infections comprise an acronym of infections that are encountered in obstetrics and neonatology, which can increase the morbidity and mortality of neonates, and can be evident at birth or even later in life during their adolescent years. There are a number of pathogens responsible for intrauterine and postpartum infections, such as parvovirus B19 and varicella-zoster virus; however, physicians must discern whether a specialized screening process for neonates with specific findings suspicious for a congenital TORCH infection is a valid approach [1-3]. Rather, the clinician should test infants based upon the clinical presentation for these specific pathogens. Most experts, such as The American College of Obstetricians and Gynecologists (ACOG) [4], currently recommend screening pregnant woman for rubella and syphilis at the first prenatal visit. Clinicians must be well acquainted with the presentations of these infections so proper diagnosis can be obtained and treatment can be initiated, thus decreasing the likelihood of mortality and childhood morbidity.

Clinical Features of TORCH Infections

Common clinical manifestations that are suggestive of specific congenital infections in the neonate are listed in Table 1.

<table>
<thead>
<tr>
<th>Infection</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxoplasmosis</td>
<td>- Intracranial calcifications in a diffuse pattern</td>
</tr>
<tr>
<td></td>
<td>- Hydrocephalus</td>
</tr>
<tr>
<td></td>
<td>- Chorioretinitis</td>
</tr>
<tr>
<td></td>
<td>- Mononuclear CSF pleocytosis or elevated CSF protein</td>
</tr>
<tr>
<td>Rubella</td>
<td>- Cataracts, glaucoma, pigmented retinopathy</td>
</tr>
<tr>
<td></td>
<td>- Congenital heart disease (patent ductus arteriosus and peripheral pulmonary artery stenosis)</td>
</tr>
<tr>
<td></td>
<td>- Radiolucent bone disease</td>
</tr>
<tr>
<td></td>
<td>- Sensorineural hearing loss</td>
</tr>
<tr>
<td>Cytomegalovirus (CMV)</td>
<td>- Periventricular intracranial calcifications</td>
</tr>
<tr>
<td></td>
<td>- Microcephaly</td>
</tr>
<tr>
<td></td>
<td>- Thrombocytopenia</td>
</tr>
<tr>
<td>Herpes Simplex Virus (HSV)</td>
<td>- Mucocutaneous vesicles or scarring</td>
</tr>
<tr>
<td></td>
<td>- CSF pleocytosis</td>
</tr>
<tr>
<td></td>
<td>- Thrombocytopenia</td>
</tr>
<tr>
<td></td>
<td>- Elevated liver transaminases</td>
</tr>
<tr>
<td></td>
<td>- Conjunctivitis or keratoconjunctivitis</td>
</tr>
<tr>
<td>Syphilis</td>
<td>- Skeletal abnormalities such as osteochondritis and periostitis</td>
</tr>
<tr>
<td></td>
<td>- Pseudoarthritis</td>
</tr>
<tr>
<td></td>
<td>- Persistent rhinitis</td>
</tr>
<tr>
<td></td>
<td>- Maculopapular rash (most notably on palms and soles or in diaper area)</td>
</tr>
</tbody>
</table>

Table 1: Clinical Features Associated with TORCH Infections.

Toxoplasmosis is a disease caused by the protozoan parasite called Toxoplasma gondii. Of note, congenital disease results from primary infection during pregnancy, specifically during the third trimester. Unlike other congenital infections that tend to manifest around 8-15 weeks of gestation, a period involving organogenesis, toxoplasmosis infectivity increases with gestational age. Maternal toxoplasma infection is most commonly acquired through ingestion of contaminated undercooked meat and meat products, soil-contaminated fruits and vegetables, or unfiltered contaminated water with the bradyzoites of the parasite. These parasites have the capability of shedding within the alimentary canal of cats, and after incidental maternal ingestion through handling and cleansing of cat litter, disseminate hematogenously to the uterine vasculature eventually entering the placenta and infecting the fetus [5,6].
After invading the fetus, these parasites invade the brain and muscle cells, forming cysts that can remain dormant for years [7]. Acute maternal infection tends to portray an asymptomatic clinical picture, and when symptoms do occur, they tend to be non-specific. These non-specific symptoms include a low-grade fever, fatigue, headache, malaise, myalgia and lymphadenopathy. Pregnant women who experience a mononucleosis-like illness should always be tested for heterophile antibodies. If these antibodies are negative, toxoplasmosis testing should be pursued.

Diagnosis is based on assessing toxoplasma specific immunoglobulins polymerase chain reaction (PCR). If these tests are negative but the clinical suspicion is high, treatment should still pursue. Prenatal treatment would include a course of pyrimethamine plus sulfadiazine [8]. Of importance, even without maternal treatment, most infants infected with toxoplasmosis do not appear to have congenital abnormalities and most often are entirely asymptomatic. Less than 10 percent of infected neonates present with a classic triad consisting of chorioretinitis, hydrocephalus and intracranial calcifications. Symptomatic infants may present with this classical triad, along with seizures, jaundice, hepatosplenomegaly, lymphadenopathy, anemia, thrombocytopenia, and abnormal CSF findings [9]. Figure 1 portrays an image of a neonate with clinical evidence of symptomatic congenital toxoplasmosis. Unlike adults or immunocompromised hosts with primary toxoplasmosis infection, who classically present with hyperechoic round CNS lesions that are most often solitary, CNS lesions in neonates are mainly comprised of calcifications around the lateral ventricles of the brain.

Figure 1: Clinical manifestations of congenital toxoplasmosis. [Courtesy of the Atlas of Infectious Diseases of the Female Genital Tract; Philadelphia: Lippincott Williams & Wilkins, 2005].

Undiagnosed and untreated neonates with congenital toxoplasmosis may present with late manifestations consisting mainly of neurologic abnormalities. An astute physician is one who is able to make a timely diagnosis, allowing for the initiation of early therapy. If a newborn is suspected of having congenital toxoplasmosis, the evaluation should include a panel consisting of a complete physical examination, T. gondii serology and evaluation for neurologic and ophthalmologic manifestations. As mentioned previously, if the newborn has characteristic clinical findings, congenital toxoplasmosis is confirmed or highly suspected based on the evidence of specific immunoglobulins T. gondii within the serum of the newborn [10]. Serial serology may be necessary in infants without clinical manifestations in order to confirm or exclude the diagnosis. Figure 2 clearly demonstrates a CT scan with small, calcified lesions demonstrating congenital toxoplasmosis with intracranial calcifications [11].

Figure 2: Brain CT scan showing small, calcified lesions demonstrating congenital toxoplasmosis with intracranial calcifications.

Children with untreated and symptomatic congenital toxoplasmosis often go on to develop serious long-term neurologic sequelae. These sequelae often consist of seizures, intellectual impairment, motoric disorders, impaired vision, hearing deficits and hydrocephalus [12]. The preferred treatment regimen involves a one-year course of pyrimethamine plus sulfadiazine and folinic acid [13]. See Table 2 for a list of treatment options during pregnancy. During the course of therapy, complete blood counts should be monitored to evaluate for signs of drug-induced neutropenia, and monitoring for late ophthalmologic and neurodevelopmental manifestations.

**Congenital Rubella**

Intrauterine infection with rubella virus is referred to as congenital rubella infection (CRI) or syndrome. This syndrome includes a variety of constellations of birth defects. These defects consist of non-specific signs and symptoms, including cataracts/congenital glaucoma and congenital heart disease, most commonly patent ductus arteriosus or peripheral pulmonary artery stenosis. Other findings commonly seen with CRI include hearing impairment and pigmented retinopathy. Less commonly, these neonates may present with purpura, hepatosplenomegaly, jaundice, microcephaly, developmental delay, meningoencephalitis and radiolucent bone disease.
Unlike toxoplasmosis, if a pregnant woman acquires an infection with rubella earlier in pregnancy, the worse are the prognosis and neonatal complications. Transmission to the fetus occurs via maternal hematogenous spread to the placenta, which typically occurs 5-7 days after maternal inoculation. After the virus invades the placental barrier, it spreads throughout the fetus via their vascular system. The congenital defects that result from infection is secondary to the cytopathical damage ensued to the blood vessels. This in turn results in ischemia of the affected organs [14,15]. The risk of maternal-fetal transmission is the greatest in the first 10 days after gestation, with cardiac and eye defects typically resulting when maternal infection occurs prior to 8 week. Hearing loss is typically observed in infections up to 18 weeks of gestation [16]. Figure 3 shows cataracts resulting from congenital rubella syndrome.

Antenatal evaluation should include a full review of the mother’s obstetrical history to assess for evidence of rubella immunity. Most experts, such as The American College of Obstetricians and Gynecologists (ACOG) [4], currently recommend screening pregnant woman for rubella and syphilis at the first prenatal visit. The clinician should also obtain a complete blood count and platelet count, long bone radiographs, ophthalmology consult, audiologic evaluation, neuroimaging and lumbar puncture to rule out CNS involvement [17].

CRI may be suspected clinically, but is confirmed with laboratory tests. Confirmation of CRI is typically followed through any of the following methods:

- Isolation of the rubella virus in culture.
- Demonstration of rubella-specific IgM antibodies.
- Demonstration of rubella-specific IgG antibodies that persist at a higher concentration or longer duration than expected from mere passive transfer of maternal antibodies.
- Detection of rubella virus RNA by reverse-transcriptase polymerase chain reaction.

As for treatment, unfortunately, treatment with antiviral or biologic agents does not alter the clinical course of CRI. Supportive care and surveillance is the only recommended option available at this time. Close monitoring within the first 6 to 12 months of life is recommended; particularly for the evaluation of hearing impairment [18]. Prevention is considered the most important aspect as far as the management of CRI concerned. Preventive measures include recommended immunizations, testing of pregnant women for rubella immunity and proper counseling regarding avoiding exposure. See Table 2 for a list of treatment options during pregnancy.

**Congenital Cytomegalovirus (CMV)**

In terms of TORCH infections, cytomegalovirus is considered the most common cause of congenital infection. CMV is a ubiquitous virus and a member of the Herpes-viridae family. An increased risk of transmission exists for mothers through primary infection, contact with toddlers in the childcare setting, infected family members, sexual intercourse and through organ transplantation and blood product administration. In underdeveloped countries, such as Africa, most children are infected by the age of three, whereas in developed countries such as the United States, as many as 60-80 percent of the population will have positive serology testing for CMV by adulthood [19]. In general, congenital infection ranges from 0.2 to 1.5 percent of all live births with any kind of congenital infection. Primary maternal infection during pregnancy can portray a transmission rate as high as 40 percent [20].

Clinical manifestations of congenital CMV infection are broad and non-specific. These include infants that are small for gestational age (SGA), hepatosplenomegaly, microcephaly, petechiae and purpura. Approximately 85 percent of newborns with congenital CMV infection can be asymptomatic at birth, however approximately 15 percent will develop progressive hearing loss and visual impairment as they age [21,22]. CNS symptoms can consist of chorioretinitis, seizures and sensorineural hearing loss [23].

Laboratory diagnosis should focus on assessing for hemolytic anemia, elevated levels of transaminases, thrombocytopenia and elevated direct and indirect bilirubin [23]. This evaluation should also aim at isolating the virus in samples of the urine or saliva within the first three weeks of life. It is also possible to detect CMV DNA in the urine and serum of newborns using polymerase chain reaction (PCR) techniques. The latter method is less available, more expensive, and often less reliable when compared to traditional cell culture [24,25]. Figure 4 demonstrates periventricular calcifications noted on CT imaging of a newborn’s infected with CMV. Other radiological brain abnormalities that can be seen with this infection include periventricular leukomalacia, ventriculomegaly and hydranencephaly [26].

Treatment of neonates with congenital CVM disease remains a controversial topic. Newborns that may benefit from long-term antiviral therapy include those with sensorineural hearing loss and congenital microcephaly [27]. Recommended treatment for neonates with symptomatic congenital CMV infection, specifically if there is CNS involvement, consists of a six week treatment course using ganciclovir. This medication is given intravenously at a dose of 6 mg/kg every 12 hours in order to achieve protection against hearing
impairment and developmental deterioration [19]. Valganciclovir is an oral version of the same therapy that can be administered at 16 mg/kg twice daily. See Table 2 for a list of treatment options during pregnancy. Figure 5 illustrates an algorithm for the diagnosis and management of congenital CMV infection.

Bone marrow suppression is a common side effect encountered with the use of ganciclovir, which is dose-dependent and reversible. Related findings include leukopenia, anemia, neutropenia and thrombocytopenia. These patients should have their blood counts monitored closely if they are receiving ganciclovir. Renal insufficiency is another possible manifestation since the drug is excreted through the urine and the dose should be adjusted if renal insufficiency or failure is present.

**Congenital Herpes Simplex Virus**

Herpes simplex virus (HSV) infection during pregnancy can pose a serious threat to the developing fetus and the newborn infant. Chapter 8 strictly outlines the diagnosis, clinical features and management of genital herpes during pregnancy. Transmission typically occurs via direct contact between the neonate and an infected maternal genital tract. If the primary HSV infection was acquired during pregnancy, then the risk of transmission is greater as compared with reactivation of a previous infection. Of special note, active genital tract infection at the time of labor is the biggest risk factor for transmission to the neonate. Transmission most commonly occurs through asymptomatic shedding of the virus to the neonate. In general, estimates related to the incidence of neonatal HSV infection ranges from 1 in 3200 to 1 in 10,000 births [28-30].

HSV is a member of the *Herpes viridae* family of viruses and enters the host through the inoculation of oral, genital, or conjunctival mucosa. Inoculation also can occur through breaks in the skin. Dissemination of the virus eventually allows the virus to reach the dorsal root ganglia, where it remains dormant for the rest of the host’s life. Of note, antiviral drugs do not affect latent HSV infection and therefore infection is life-long [31].
Intrauterine HSV is a rare occurrence and most likely is caused by maternal viremia associated with primary infection during pregnancy. Intrauterine infection is associated with hydropsfetalis and in-utero fetal demise. The characteristic triad noted at birth includes skin lesions consistent of vesicles, ulcerations or scarring (Figure 6) [32]; eye damage and CNS abnormalities, such as hydranencephaly and microcephaly. This characteristic triad evidently occurs in less than one-third of cases [33-35].

![Figure 6: Congenital Herpes Simplex Virus Infection.](image)

About 45 percent of infected neonates with HSV are accounted for by skin, eye and mouth disease (SEM Disease) [36]. This typically presents during the first two to six weeks of life and may appear to be a benign disease at first, however if not treated, the disease may progress to the CNS or other organs. A coalescing or clustering of vesicles, with an associated erythematous base, usually characterizes SEM disease. Often times, vesicles may cluster at the presenting part of the body, such as the scalp (Figure 7) [31].

![Figure 7: Neonatal HSV Fetal Scalp Infection of the SEM type.](image)

Early signs of HSV infection involving the neonate’s eye include excessive tearing, eye pain, conjunctival erythema and periorbital skin vesicles. The presence of HSV keratoconjunctivitis may progress to cataracts, chorioretinitis and eventually permanent vision loss [31]. Early diagnosis and treatment is highly recommended for any neonate who presents with any evidence suspicious for SEM disease.

Neonatal HSV CNS disease accounts for about one-third of neonatal HSV cases and may manifest as focal or generalized seizures, irritability, lethargy, tremors, poor feeding, temperature instability (fever/hypothermia) or full anterior fontanel [36]. Clinical manifestation can arise any time during the first six weeks of life, but usually occurs within the first month of life [13]. Classic CSF findings include a mononuclear cell pleocytosis, normal or slightly low glucose concentration and moderately elevated protein level. Electroencephalogram (EEG) is often abnormal from early on in the disease and may show focal or multifocal periodic epileptic form discharges [31,37]. Neuroimaging studies may show parenchymal brain edema, hemorrhage or destructive lesions in the temporal frontal, parietal or brainstem regions in the brain [31]. Mortality exceeds 80 percent in cases of untreated disseminated neonatal HSV (Figure 8) [31,38].

Diagnosis of neonatal HSV infection can be established through any of the following methods:

- Isolation of HSV in culture
- Detection of DNA via PCR assays
Detection of HSV specific antigens using rapid direct immunofluorescence or enzyme immunoassays.

A negative result of any of these tests does not rule out a diagnosis of neonatal HSV, and therefore all suspected cases should receive an EEG and neuroimaging studies to screen for involvement of the CNS.

The recommended antiviral agent for treatment of neonatal HSV infection is acyclovir at a dose of 60 mg/kg per day intravenously divided every eight hours. It is important that treatment be initiated at the time neonatal HSV is suspected and continued while results of clinical and imaging evaluations are pending. Localized SEM disease should be treated for a minimum of 14 days while disseminated and CNS disease should be treated for a minimum of 21 days [13,31]. Neonates with ocular involvement should receive a topical ophthalmic solution and ophthalmology consultation in addition to systemic acyclovir therapy. Oral acyclovir is used for suppressive therapy at a dose of 300 mg/m2 per dose three times a day for six months after intravenous treatment is completed. See Table 2 for a list of treatment options during pregnancy.

![CT Head Imaging of the Brain of a Four-Week-Old Infant with CNS Herpes Simplex Viral Infection. (Courtesy of Gail Demmler-Harrison, MD, Texas Children’s Hospital)](image)

<table>
<thead>
<tr>
<th>Infection</th>
<th>Treatment</th>
<th>Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxoplasmosis</td>
<td>Pyrimethamine: 50mg twice daily for 2 days then 50mg daily. PLUS Sulfadiazine: 75mg/kg/daily in two divided doses for 2 days then 50mg/kg/twice daily PLUS Folinic Acid: 10-20mg daily</td>
<td>Spiramycin: 1 gram IV every 8 hours</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>Ganciclovir* 5mg/kg IV every 12 hours for 14 days OR Valganciclovir* 900mg PO daily for 3-6 months OR CMV-specific hyperimmune globulin (200 units/kg of body weight)*</td>
<td>If Blood Transfusions Needed: CMV-negative blood</td>
</tr>
<tr>
<td>Rubella</td>
<td>Prevention Only</td>
<td>Rubella Vaccine prior to planned pregnancy within 4 weeks</td>
</tr>
<tr>
<td>Herpes Simplex Virus</td>
<td>Acyclovir 400mg PO twice Daily</td>
<td>Acyclovir 400mg PO twice Daily OR Famiclovir 250mg PO twice Daily OR Valaclovir 500mg PO Daily</td>
</tr>
</tbody>
</table>

*Limited Studies Have Shown Success Rate During Pregnancy

Table 2: Treatment Options for TORCH Infections During Pregnancy.

Acknowledgment
The author of this chapter would like to thank Dr. Bassam Husam Rimawi for assistance in writing this chapter.

References