Congenital Toxoplasmosis and Congenital Cytomegalovirus Infection

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Although congenital infections traditionally have been grouped together under the acronym TORCH (Toxoplasmosis, “Other,” Rubella, Cytomegalovirus [CMV], and Herpes simplex virus), this term promotes the idea that congenital infections are indistinguishable from each other. Although they share common clinical features, these infections have distinctive features that generally can be used to distinguish one infection from another on clinical grounds. It is of utmost importance for pediatricians to be aware of the prominent features of each congenital infection rather than considering them as a group.1

It is still common in pediatric nurseries and wards in the United States to find the request “TORCH titer” written on the chart of a patient in whom a congenital infection is under consideration. This term is erroneous, as there are specific serologic and diagnostic tests for each of these congenital infections. The appropriate tests should be requested based on clinical suspicion for which infectious agent is most likely involved.

It is also important to remember that most congenital infections arise from primary maternal infections that are subclinical or have no specific symptoms, and therefore the maternal history is not helpful in identifying newborns at risk. This makes prenatal care of extreme importance, especially awareness of maternal immunologic status against the most common pathogens implicated in congenital infections.

This manual will discuss two of the most important and common infections acquired in utero by newborns—Toxoplasmosis and CMV. Although these infections share similar features, there are striking differences that in most cases allow differentiation from one another. CMV is the most common congenital infection seen in the United States; therefore, pediatricians must be familiar with its clinical presentation, diagnosis, and sequelae. Although toxoplasmosis is less common in the United States than other parts of the world, it presents a significant clinical challenge when encountered. In both of these infections, the majority of infected patients are asymptomatic at birth, and failure to diagnose the condition increases the potential of developing sequelae later in childhood or adolescence that can carry significant challenges to the patient’s quality of life.

CONGENITAL TOXOPLASMOSIS

CASE 1 PRESENTATION

A 2-hour-old male newborn, product of an uncomplicated vaginal delivery at 39 weeks gestational age (by dates), is admitted to the routine care nursery. He was born to a 23-year-old mother with her first pregnancy. The mother had only 1 prenatal care visit but otherwise reported an uneventful pregnancy. The infant is examined initially by a nurse, who records the patient’s head circumference as above the 95th percentile for his age. In addition, she observes a petechial rash. She does not notify a physician immediately of these findings. A physician is called to evaluate the patient when the same nurse finds him having a generalized tonic-clonic seizure. The seizure lasts approximately 3 minutes and stops without intervention. The physical examination at that point shows a patient with diffuse petechiae and moderate jaundice, a palpable spleen, and a palpable liver approximately 3 cm below the right costal margin.

- What is the initial diagnostic plan for this newborn?
- Are there any imaging studies needed?

DIFFERENTIAL DIAGNOSIS

This patient exhibits findings (hepatosplenomegaly, petechial rash) that may be seen with several congenital infections. When symptomatic, however, each of the infections usually includes unique clinical features as well. The presence of macrocephaly in a newborn who is adequately sized for gestational age, as in this case, is highly suggestive of Toxoplasma gondii congenital infection. Symptomatic congenital CMV infection is perhaps the clinical entity that most closely resembles congenital
Toxoplasmosis. Although on occasion, CMV infection can present with macrocephaly, this is rather rare, microcephaly being one of its most common presenting features. CMV-infected children who are symptomatic also are very likely to have intrauterine growth retardation and be small for gestational age, another feature that is helpful in distinguishing this infection from symptomatic congenital toxoplasmosis.

This patient should undergo serologic and polymerase chain reaction (PCR) analysis for congenital *T. gondii* infection. Imaging studies, such as ultrasonography and/or computed tomography (CT) also should be performed. These studies will help to determine the presence of hydrocephaly and intraparenchymal brain calcifications, findings classical of toxoplasmosis.

**GENERAL CONSIDERATIONS**

**Natural History and Transmission**

*T. gondii* is the causative agent of toxoplasmosis. It is an obligate intracellular parasite that has been found in domestic and wild animal species. Its complex life cycle includes a sexual stage that occurs exclusively in cats, which act as a primary host, and an asexual cycle that can occur in most other animals. The asexual stage of the cycle comprises a rapidly dividing form (tachyzoite) that occurs in the acute phase of infection and a slowly growing form (bradyzoite) observed in tissue cysts. The sexual stage of the cycle occurs in the feline gastrointestinal tract and culminates with the excretion of oocysts.

Human infection typically results from ingestion of either oocysts or bradyzoites. Oocysts are ingested either from handling cat litter or soil contaminated with cat feces or from consuming contaminated foods, such as unwashed vegetables. Bradyzoites are ingested by handling or eating raw or undercooked pork or beef. Rarely, infection can result from the transmission of tachyzoites during a blood transfusion or by an accidental laboratory inoculation.

After ingestion, enzymatic degradation in the gastrointestinal tract releases bradyzoites from cysts and sporozoites from oocysts. These rapidly invade the surrounding endothelial cells and become tachyzoites, which are the invasive form of *T. gondii*. Tachyzoites disseminate within hours to other parts of the body, dividing asexually and releasing additional tachyzoites to infect other cells. In immunocompetent hosts, enduring cellular and humoral immunity develops within 7 to 10 days of infection and chronic infection ensues, marked by the appearance of bradyzoites, which can remain encysted in host tissues indefinitely, chronic infection with the organism confers protection to reinfection.

In an immunocompetent mother, maternal-fetal transmission occurs in the form of tachyzoites only, not bradyzoites. This means that the fetus is at risk if maternal infection occurs during pregnancy but not if the mother is chronically infected from a previous exposure. The most favorable conditions for transmission to the placenta are present when the onset of parasitemia occurs before the development of an adequate immune response by the mother and when the placental blood flow is well developed, as is the case during the last trimester of pregnancy. The incidence of fetal infection, therefore, relates to the stage of pregnancy during which the mother acquires the infection, with fetal infection rates increasing from 15% during the first trimester to 65% during the third trimester. The risk of severe manifestations, however, is inversely related to gestational age at the time of initial maternal infection; almost no manifestations of disease are present at birth if infection occurred after the 26th week of gestation.

**Epidemiology**

Toxoplasmosis is found throughout the world, but its prevalence varies markedly by geographic area. The highest prevalence rates have been found in Central Africa, Central America, Tahiti, and France. These are regions where there are many cats that live outdoors, where the environment is warm and humid, or where eating undercooked meat is customary.

In the United States, the incidence of acute toxoplasmosis infection during pregnancy has been estimated at 0.2% to 1%. The incidence of congenital toxoplasmosis infection has been estimated to range from 1 in 1000 to 1 in 8000 live births.

**CLINICAL MANIFESTATIONS**

**Clinical Manifestations in the Mother**

Symptomatic patients typically present with a “mono-nucleosis-like illness,” with cervical adenopathy, fever, malaise, pharyngitis, and lymphocytosis. The infection is self-limited. Only 10% of pregnant mothers who acquire acute *Toxoplasma* infection have symptoms of the infection. In the remainder, symptoms are so mild that they are likely to escape recollection. Symptoms of infection during pregnancy therefore cannot be used as a screening tool for the possibility of congenital infection.

**Clinical Manifestations in the Newborn**

The severity of symptoms in the newborn depends greatly on the time of infection during the gestational period. It is estimated that of all newborns born with congenital toxoplasmosis, 75% are initially asymptomatic,
In approximately 60% of symptomatic infants, disease is limited to the central nervous system (CNS) and the eye. These infants typically present with hydrocephaly, intracranial calcifications, seizures, chorioretinitis, and pleocytosis and elevated protein levels in the cerebrospinal fluid (CSF). Approximately 30% of symptomatic patients have additional generalized findings such as hepatosplenomegaly, lymphadenopathy, jaundice, anemia, and thrombocytopenia. The remaining 10% have ocular disease alone.

Infants born with subclinical infection represent a great diagnostic and management challenge. Although their disease is not clinically apparent, numerous abnormalities may be encountered on CNS and ophthalmologic evaluation. In a study conducted from 1986 to 1992, 52 out of 635,000 infants were found to be infected with congenital toxoplasmosis. Fifty of these infants (96%) had normal clinical examination results in the newborn period. After their infection status was established, 48 of them underwent CNS and retinal evaluations, and abnormalities were encountered in 19 (40%). Patients with neurologic manifestations may present later in life with psychomotor retardation, seizures, persistent cerebellar disfunction, and sensorineural hearing loss (SNHL). Those with ophthalmologic involvement will present with retinal lesions and visual loss, sometimes as late as the second or third decade of life.2

**DIAGNOSIS**

**Prenatal Diagnosis**

In the United States, universal screening of pregnant women for *Toxoplasma* infection is not implemented, and maternal infection is usually diagnosed only when the clinical findings are suggestive of acute toxoplasmosis or when a routine serologic screen is obtained.2

Evaluation for fetal *T. gondii* infection is recommended when acute maternal infection is diagnosed. The methods designed to detect congenital infection include ultrasonographic imaging, culture or PCR analysis of amniotic fluid, and determination of the fetal immune response or isolation of the organism via percutaneous umbilical blood sampling (PUBS). A combination of imaging, amniocentesis, and PUBS may be used for a more accurate diagnosis.3,4,5 PCR analysis of amniotic fluid has shown greater than 95% sensitivity in diagnosing fetal *T. gondii* infection and has become the procedure of choice over the last few years.3,4,5 Ultrasound findings suggestive of fetal *Toxoplasma* infection include ventriculomegaly, intracranial calcifications, hepatosplenomegaly, ascites, and a thickened placenta.3,4

Fetal blood can be obtained through PUBS and sent for analysis of *T. gondii*-specific IgA, IgM, and IgE or for isolation of the parasite. The diagnosis of fetal infection prior to 20 weeks through PUBS is not recommended, however, both because of technical difficulties and because the fetus’s immature immunologic system is unlikely to have produced IgA or IgM.3,5 Direct inoculation of cord blood or amniotic fluid into a mouse can be used to isolate the parasite, but it may take up to 6 weeks for a confirmed diagnosis, and the sensitivity of this technique is 70% at best.3,5

**Diagnosis in the Newborn**

Several methods are available to aid in the diagnosis of congenital toxoplasmosis in newborns. Isolation of the organism from the placenta or from the infant’s tissues is diagnostic; however, this method is problematic because it requires a reference laboratory and may take up to 6 weeks for confirmation. Serologic methods are therefore most commonly used.2

A wide variety of serologic tests for detection of anti-*Toxoplasma* IgG, IgM, IgA, and IgE antibodies are available, and a combination of several of these is perhaps the best approach to diagnosis.3,5 A positive IgG titer is sufficient in most instances for determining that a patient has been infected. Because titers of IgM and IgA may remain present for more than 12 months, a single positive result of either of these tests is not informative regarding when infection took place. For this reason, it is recommended that serologic specimens be obtained serially at least 3 weeks apart to make a diagnosis of acute infection.3,5

Table 1 summarizes the different serologic tests available for the diagnosis of congenital or acquired toxoplasmosis.2

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG, IgM, IgA, IgE</td>
<td>95%</td>
<td>90%</td>
</tr>
<tr>
<td>PCR analysis of amniotic fluid</td>
<td>90%</td>
<td>95%</td>
</tr>
<tr>
<td>Culture or PCR of amniotic fluid</td>
<td>90%</td>
<td>95%</td>
</tr>
</tbody>
</table>

**Imaging Studies**

Ultrasound, CT, and magnetic resonance imaging are very useful tools when evaluating a child who may have congenital toxoplasmosis involving the CNS; these studies are therefore routinely ordered where available. Several imaging and sonographic signs have been described in confirmed cases, including ventriculomegaly,
calcifications, and multicystic encephalomalacia. Calcifications generally are distributed throughout the brain parenchyma (Figure 1). (In contrast, calcifications in patients with congenital CMV infection usually occur in the periventricular areas.)

**FOLLOW-UP DISCUSSION OF CASE 1**

The mother is asked about her recollections of any illness during pregnancy, as well as about her eating habits, pets, the location of her home, and her outdoor activities. Upon questioning, she recalls having had a “flu-like illness” about 2 months after she found out she was pregnant, but it went away and she thought no more about it. She owns no pets and has a fenced-in backyard. When questioned about her eating habits, she notes that she and her husband like to eat raw meat and that she purchases it from a local meat market. The presumptive diagnosis of toxoplasmosis in the newborn is then confirmed with the use of serologic testing and PCR.

- **What treatment options are available for the newborn infant?**
- **Could the infection in the newborn have been prevented with prenatal diagnosis and treatment?**
- **How could the mother have prevented infection?**

**TREATMENT**

**Antenatal Treatment and Prophylaxis**

If maternal infection during pregnancy is documented, prophylaxis with the macrolide spiramycin can be given to protect the fetus from infection. Spiramycin has not been approved in the United States for routine use, however, and can only be obtained through its manufacturer, Aventis Pharmaceuticals (Bridgewater,

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**Table 1. Serologic Diagnosis of Toxoplasma Infection**

<table>
<thead>
<tr>
<th>Test</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immunoglobulin G</strong></td>
<td></td>
</tr>
<tr>
<td>Sabin-Feldman dye test</td>
<td>Utilizes uptake of the dye methylene blue by the <em>Toxoplasma</em> tachyzoite. The tachyzoite lyses in the presence of specific IgG and IgM antibody. Gold standard for the diagnosis of toxoplasmosis. Sensitive and specific. Requires live organisms and only can be performed at reference labs. Detectable 2 weeks postinfection. Low titers persist for life.</td>
</tr>
<tr>
<td>Indirect fluorescent antibody test (IFA)</td>
<td>Titers measured are comparable to Sabin-Feldman dye test in reference labs. Commercially available but results are laboratory-dependent and may be prone to false results. Used more widely than the dye test.</td>
</tr>
<tr>
<td><strong>Immunoglobulin M</strong></td>
<td></td>
</tr>
<tr>
<td>Enzyme-linked immunosorbent assay (ELISA)</td>
<td>The double-sandwich IgM ELISA is the most sensitive test. IgM antibodies detected by this method appear early; because they do not cross the placenta, IgM antibodies are useful in determining congenital infection. Positive results from a commercial laboratory require confirmation by a reference laboratory.</td>
</tr>
<tr>
<td>IFA</td>
<td>Not as sensitive as IgM ELISA. Rheumatoid factor and antinuclear antibodies may give false-positive results.</td>
</tr>
<tr>
<td>Immunosorbent agglutination assay (ISAGA)</td>
<td>Uses formalin-fixed organisms or antigen-coated latex particles to detect IgM antibodies. Test can be complementary to ELISA. Positive results from commercial laboratories require confirmation by a reference laboratory.</td>
</tr>
<tr>
<td><strong>Immunoglobulin A</strong></td>
<td></td>
</tr>
<tr>
<td>ELISA</td>
<td>Useful in determining congenital infection because IgA does not cross placenta. IgA ELISA appears to be more sensitive than IgM ELISA for the diagnosis of congenital <em>Toxoplasma</em> infection in both newborns and fetuses.</td>
</tr>
<tr>
<td>ISAGA</td>
<td>Complementary method for detection of IgA.</td>
</tr>
<tr>
<td><strong>Immunoglobulin E</strong></td>
<td></td>
</tr>
<tr>
<td>ELISA</td>
<td>Duration of detectable IgE antibodies may be shorter than for IgA and IgM antibodies; therefore, IgE detection is a useful tool for determining recent infection. May be useful for determining congenital infection from a single serum sample when used in combination with IgA and IgM antibody determinations.</td>
</tr>
<tr>
<td>ISAGA</td>
<td>Complementary method to ELISA for detection of IgE.</td>
</tr>
</tbody>
</table>
NJ), after approval on an individual basis from the US Food and Drug Administration. The administration of spiramycin (1 g 3 times daily) has been shown to decrease the frequency of maternal transmission to the fetus by 50% and is currently recommended in several European countries. The justification for the treatment is based on belief by many experts that after maternal infection, the parasite is not passed immediately to the fetus, but remains for several weeks in the placenta, providing a window of opportunity for prophylaxis. Experimental data suggest that once the placenta is infected it remains infected for the duration of the gestational period; it is therefore recommended that spiramycin be continued for the length of the pregnancy.

Spiramycin is safe for the fetus, and the most common side effects in the mother pertain to the gastrointestinal tract. Because spiramycin does not affect Toxoplasma cysts, it must be given before fetal infection has occurred.

If diagnostic testing reveals that the fetus is already infected, sulfadiazine and pyrimethamine are given to treat the fetal infection. Sulfadiazine is given to the mother at a dose of 1.5 g twice daily. Pyrimethamine is given at a dose of 100 mg twice daily the first day and 50 mg daily thereafter. Folinic acid (leucovorin) at a dose of 10 to 20 mg daily is added to decrease pyrimethamine toxicity. This combination can be alternated every 3 weeks with spiramycin until completion of the pregnancy. The mother must be monitored closely for hematologic toxicity.

Treatment in the Newborn

In 1994, McAuley and colleagues reported the results of the largest existent series of congenital toxoplasmosis patients who received treatment after birth. The study patients received pyrimethamine at a dose of 1 mg/kg body weight daily for 2 to 6 months followed by 1 mg/kg every other day to complete 1 year of therapy. In addition to the pyrimethamine, sulfadiazine was given at a dose of 50 mg/kg twice daily for 12 months. Leucovorin (10 mg 3 times/week) was administered to prevent pyrimethamine toxicity. This group of patients was compared with untreated control patients. On follow-up 3 to 6 years later, 8% of the treated patients had developed new retinal lesions compared with 29% of untreated patients. Neurologic outcomes also were dramatically improved with treatment: the number of treated patients with significant neurologic symptoms was reduced from 57% pre-treatment to 24% post-treatment. The control patients did not show any neurologic improvement.

This regimen has now become the standard of therapy for newborns with symptomatic congenital toxoplasmosis infection. It is recommended that complete blood counts be performed 1 to 2 times weekly while on daily pyrimethamine and 1 to 2 times monthly while on every-other-day pyrimethamine therapy. This is to monitor for neutropenia, the most common side effect of pyrimethamine therapy. It also is recommended that a serum glucose-6-phosphate dehydrogenase screen be performed prior to initiating sulfadiazine.

Follow-up of infants with symptomatic congenital toxoplasmosis should include periodic pediatric evaluations, always placing emphasis on neurodevelopmental issues; evaluations by a pediatric neurologist every 3 months until 1 year of age; and pediatric ophthalmology evaluation every 3 months until 18 months of age.

PREVENTION

Although some European countries routinely screen for Toxoplasma infection during pregnancy, there is no screening program available in the United States. One reason for this is the low prevalence of toxoplasmosis in this country. In addition, the false-positive rate for serologic screening performed in commercial laboratories is high, allowing the potential for abortion of normal fetuses. In addition, interpretation of serologic
data is not easy. IgM antibody against *Toxoplasma* can remain elevated for several months after infection and its detection may signify preconception infection (and thus a low risk of transmission to the fetus) rather than infection during pregnancy. In addition, IgG can remain elevated for many years.3,10

Perhaps the best approach is to limit screening to pregnant mothers with symptoms or those with suspicious ultrasound findings. Positive results should always be confirmed by a reference laboratory with experience on diagnosis of the infection.3

It is important to inform pregnant women of preventive measures for reducing the risk of *Toxoplasma* infection. The majority of human infections come from eating undercooked meat, and that practice is perhaps the most important to avoid.

**SUMMARY**

Congenital toxoplasmosis is rare in the United States, but it does occur. Although traditionally considered a severe generalized infection, only a small percentage of patients present in such a manner. Most present with subtle or no symptoms present at birth, and the infection can remain undiscovered until late in infancy or even early adult life. The diagnosis usually is made through the use of complex serology, and is confirmed by PCR assays performed in specific reference laboratories.

If a pregnant woman is diagnosed with *Toxoplasma* infection during her pregnancy, anti-infective treatment should be administered as early as possible to prevent transmission to the fetus, or to treat the fetus if fetal infection already has occurred. *Toxoplasma*-infected newborns should be administered prompt treatment to reduce the risk and severity of neurologic and ophthalmologic sequelae. These measures do not, however, offer absolute cure, and thus preventing exposure to *T. gondii* is the best approach for pregnant women.

**CASE 2 PRESENTATION**

A male newborn, 37 weeks by gestational age, is brought in to the intensive care nursery shortly after birth. In the delivery room, he was noted to be very small for his gestational age, with a weight of only 1850 g, and microcephalic. He also was noted to be jaundiced and to have a diffuse petechial rash. His liver and spleen are both significantly enlarged. The mother had sporadic prenatal care but no noted risk factors. Serologic screening during one of her initial prenatal care visits yielded the following results: hepatitis B surface antigen–negative, VDRL-negative, and CMV IgG– and IgM–negative. Initial blood work shows a platelet count of $50 \times 10^3 / \text{mm}^3$, a hemoglobin concentration of 9.8 g/dL, and a direct bilirubin level of 5.8 g/dL.

- What is the diagnostic work-up for this patient?
- Which clinical features in this presentation raise the suspicion of CMV infection?

**DIFFERENTIAL DIAGNOSIS**

Similar to the infant presented in case 1, this patient has features common to many congenital infections, including hepatosplenomegaly and a petechial rash. However, this newborn’s microcephaly and small size for gestational age make this presentation highly suspicious for CMV infection; these features are among those most frequently encountered when this congenital infection is symptomatic. The mother’s prenatal CMV-negative status means that she was susceptible to contracting primary CMV infection during pregnancy.

The initial work-up for this infant should include a urine shell vial culture for CMV and neuroimaging studies such as cranial ultrasonography and/or CT scan. The presence of intracranial calcifications in the periventricular space is characteristic for CMV.

**GENERAL CONSIDERATIONS**

**Natural History**

CMV is a member of the Herpesviridae family of viruses, along with Epstein-Barr virus; varicella zoster virus; human herpes viruses 6, 7, and 8; and herpes simplex virus types 1 and 2. The Herpesviridae viruses are enveloped and contain a double-stranded DNA genome surrounded by a protein icosahedral capsid. These viruses share the properties of latency and reactivation.14,15 Although distinct serotypes of CMV have not been defined, the virus can be subdivided into 4 subtypes based on variation in glycoprotein B. The subdivisions appear to correlate with tropism in vivo, and some proof exists that variation in this protein may influence the virulence of CMV.16

Humans and higher primates are the only known reservoir of the virus.14,16 Symptomatic infection in humans usually occurs in either fetuses or in individuals with defective T-cell immunity (eg, AIDS patients). CMV has the capacity to destroy host cells, to infect a wide diversity of cells and tissues, to elude and disturb host defense mechanisms, and to persist latent in the host. The ability of CMV to infect leukocytes and vascular endothelial cells likely facilitates dissemination of the virus within the host. The virus also encodes chemokines.
Congenital Toxoplasmosis and CMV Infection

Cytomegalovirus Infection During Pregnancy

More than 90% of primary CMV infections are asymptomatic and are likely to go undetected. The diagnosis is made serologically. Primary versus secondary infection during pregnancy may be differentiated on the basis of serologic testing. The presence of both IgG and IgM anti-CMV antibodies during pregnancy may be used as presumptive evidence of primary infection. The presence of maternal antibody to CMV prior to conception together with presence of CMV determined by culture in the offspring meets the definition of recurrent CMV infection in the mother. Recurrence can result from either reactivation of the woman’s original CMV strain or acquisition of a new strain of the virus.

Although the presence of maternal antibodies prior to conception does not appear to prevent transmission of CMV to the fetus, they do prevent disease in the latter. Primary infection during pregnancy is more likely than recurrent infection to produce symptoms and sequelae in the infant. In fact, only a limited number of infants with symptomatic congenital infection are known to have been born to mothers who were seropositive before pregnancy, and in most of these cases, either maternal infection occurred very shortly before conception or the mother suffered from immunosuppression.

Symptomatic primary infection with CMV is seen occasionally during pregnancy, presenting as a mononucleosis-like illness similar to that seen with the Epstein-Barr virus. Symptoms and signs include fatigue, headaches, myalgias, pharyngitis, diarrhea, cervical lymphadenopathy, hepatomegaly, splenomegaly, and rash. Appropriate serologic testing should be performed in these cases to confirm the diagnosis and rule out other conditions that can present similarly.
Most studies have shown equal rates of transmission of the virus to the fetus in all three trimesters of pregnancy. It appears, however, that severe neurologic handicaps are more likely to occur if infection occurs during the first half of pregnancy.14,15

**CLINICAL MANIFESTATIONS**

**Clinical Manifestations in the Fetus**

A fetus infected with CMV may be asymptomatic or may exhibit severe manifestations. Spontaneous first trimester abortion and fetal loss later in pregnancy can occur in women who are primarily infected during pregnancy. Fetal abnormalities detected through ultrasonography that suggest possible intrauterine CMV infection include oligohydramnios or polyhydramnios, nonimmune hydrops, hepatosplenomegaly, ascites, microcephaly, cerebral ventriculomegaly, intracranial calcifications, pleural or pericardial effusions, and or pseudomeconium ileus. Some of these manifestations (eg, ileus, effusions) may resolve in utero. These findings are nonspecific—several other congenital infections (ie, toxoplasmosis, varicella zoster virus, rubella, herpes simplex virus, syphilis) may cause similar findings. In addition some genetic and metabolic disorders also may present with similar features.14,15

**Clinical Manifestations in the Newborn**

Ninety percent of newborns who have congenital CMV infection show no clinical signs at birth and to the untrained eye are indistinguishable from noninfected newborns. Yet some studies have shown subtle difference in measurements and weight when compared with normal uninfected newborns.14,17,19,23 Approximately 15% of these asymptomatic patients will experience significant unilateral or bilateral sensorineural deafness that usually is diagnosed during the first 2 years of life.

The 10% of infected newborns with manifestations of the disease have significant evidence of infection, including intrauterine growth retardation, CNS involvement, jaundice, hepatomegaly, petechiae or purpura, thrombocytopenia, and pneumonia (Figure 2).14,19,21 Mortality in symptomatic newborns can be as high as 15%.17

The triad of hepatomegaly, splenomegaly, and petechiae is commonly seen in infants with symptomatic congenital CMV infection. Hepatomegaly usually is accompanied by mild hepatitis, although in most instances, transaminase elevations do not exceed 300 IU/mL. Hyperbilirubinemia can be impressive, however, with direct bilirubin sometimes reaching levels above 30 mg/dL. Petechiae can be seen with or without thrombocytopenia. Platelet counts may be as low as 2 x 10^9 cells/mm³, but more frequently range from 20 to 60 x 10^9/mm³.

Hepatomegaly and abnormal liver function test results usually resolve within the first few months of life, and thrombocytopenia usually resolves during the first few weeks of life. The only manifestations present at birth that do not resolve are those involving the CNS and hearing.14,17 Microcephaly may occur as part of a generalized intrauterine growth retardation or may occur in a newborn with normal weight. Intracranial calcifications can be found in close to 80% of symptomatic patients who undergo cranial ultrasonography or CT. These calcifications are usually distributed in a linear fashion and can be seen around the periventricular area. The cortical and subcortical regions and basal ganglia also may be affected.14 Other neurologic findings seen on imaging include periventricular leukomalacia, cortical atrophy, ventricular enlargement, subdural effusions, and polycystic encephalomalacia.24,25

Chorioretinitis is present in approximately 20% of cases and typically is unilateral. It is usually inactive at birth and rarely progresses postnatally.14–17 If severe, however, it can lead to strabismus, optic atrophy, and blindness.

**DIAGNOSIS**

**Diagnosis in the Fetus**

Prenatal diagnosis of fetal CMV infection in at-risk mothers (ie, those who are seronegative in pregnancy) is available through a variety of tests; however, none are sufficiently sensitive during the first half of gestation to influence fetal intervention strategies. Isolation of the virus from amniotic fluid through culture is the standard for prenatal diagnosis. But although viral culture of amniotic fluid has a specificity and positive predictive value of
close to 100%, its sensitivity is poor, and therefore a negative culture can not rule out the presence of fetal infection.\textsuperscript{14,15} The presence of CMV-specific IgM in cordocentesis samples is suggestive of infection, but sensitivity of this test ranges from 20% to 75%, and a negative result does not exclude the possibility of infection. Detection of viral DNA through PCR analysis of amniotic fluid has been used, but its presence in amniotic fluid does not necessarily imply symptomatic infection in the fetus.

**Diagnosis in the Newborn**

The diagnosis of congenital CMV infection is established by viral culture of urine, saliva, or tissue of the newborn obtained within 3 weeks of life. All newborns in which the diagnosis is suspected should have this test performed. It is essential to isolate the virus early in life in order to differentiate congenital infection from infection acquired perinatally or postnatally because the sequelae of infection are different.\textsuperscript{14,15,17}

Isolation of the virus can be accomplished by traditional cell viral culture methods, which can require up to 2 weeks for a positive result. The shell vial assay rapid culture technique is as sensitive as traditional cell culturing and results can sometimes be known in as short a time as 24 to 48 hours. This method uses centrifugation to enhance infectivity and a fluorescent monoclonal antibody to detect the presence of early antigens in infected tissue culture cells. A positive shell vial assay always should be confirmed with a traditional viral culture.\textsuperscript{14,17}

Standard serologic tests such as CMV IgG and IgM antibodies regularly are used to diagnose congenital CMV infection in newborns, but this approach has several disadvantages and its use should be discouraged. Whereas a negative CMV IgG result likely rules out infection, a positive sample is of little value because up to 80% of women of reproductive age have CMV IgG antibodies that will be passed on to their infants. A positive CMV IgM result may suggest the presence of congenital infection but is far less sensitive than a culture. In addition, a negative CMV IgM result does not rule out infection because only 30% to 89% of patients with congenital infection confirmed by viral culture have positive IgM titers.\textsuperscript{14,17} Other tests than may yield information suggestive of CMV infection include presence of type A Cowdry intranuclear inclusions in urine leukocytes, electron microscopy that identifies viral particles, and detection of CMV DNA by PCR in blood or body fluids.\textsuperscript{14,15,17} The latter appears to offer the most promise, although some experts believe that its use offers no advantage to obtaining a viral culture because infected patients shed large amounts of virus in their urine and saliva.\textsuperscript{15,17} Some studies have shown that presence of CMV DNA in CSF is strongly associated with poor neurodevelopmental outcome, and when available, PCR analysis of CSF should be performed.\textsuperscript{14,15}

**FOLLOW-UP DISCUSSION OF CASE 2**

A urine shell vial culture performed during the first week of life was interpreted as positive for CMV. This later was confirmed by a standard cell viral culture. Both cranial ultrasonography and a CT scan showed the presence of multiple intracranial calcifications, most of which were located in the periventricular space. An ophthalmologic examination showed the presence of chorioretinitis. The diagnosis of congenital symptomatic CMV was made.

- How should the patient be managed initially?
- Are there any treatment options for this patient?
- Could this patient’s condition have been prevented?

**MANAGEMENT**

**Work-up and Surveillance**

As the majority of CMV-infected fetuses will be born with no manifestations of the disease, no clear guidelines exist on how to manage cases in which infection is detected prenatally. The most prudent approach in this setting is to follow fetal growth and development through serial ultrasonography.\textsuperscript{14,15}

Once congenital CMV is diagnosed in a neonate, the patient should undergo evaluation to determine the extent of viral infection in various organ systems. A full physical examination is mandatory, recording height, weight, and head circumference ratios and measuring degree of hepatosplenomegaly. The eyes and retinas should be examined by an experienced pediatric ophthalmologist. A CT scan of the brain should be performed, and hearing should be assessed by performing brainstem-evoked response testing. Even patients without retinal lesions should continue to have periodic follow-up examinations to monitor for the development of late-onset retinitis. Hearing also should be evaluated periodically regardless of findings from the initial evaluation to monitor for late-onset or progressive hearing loss.\textsuperscript{14,15} A thorough laboratory evaluation should be performed, including a complete blood count and peripheral smear, platelet count, liver transaminase and bilirubin levels, and a complete CSF analysis.\textsuperscript{14,15}

Patients diagnosed with congenital CMV infection need long-term neurodevelopmental, ophthalmologic, and auditory follow-up.\textsuperscript{15,19} Careful developmental monitoring of infected children is crucial, and intervention as early as possible should be the norm.

Several factors, including microcephaly, intracranial
calcifications, chorioretinitis, and neurologic abnormalities at birth traditionally have been considered reliable predictors of poor neurodevelopment.\textsuperscript{15,19,25,26} A recent study as shown that of these factors, microcephaly is the most specific predictor of a poor cognitive outcome.\textsuperscript{11} Not all patients with symptomatic congenital CMV infection are likely to have abnormal intellectual and neurologic development, however. Patients with symptomatic congenital infection whose manifestations are limited to visceral and reticuloendothelial organ systems (ie, petechiae, hepatosplenomegaly, jaundice, and thrombocytopenia) and who lack intracranial calcifications and microcephaly are likely to have normal or near-normal neurodevelopment, however. For this reason, care should be taken not to generalize a poor outcome to all patients but rather use a conservative expectant approach when indicated.\textsuperscript{14}

Infants born with asymptomatic, or “silent” congenital CMV infection present a particularly difficult clinical challenge. Ten percent to 15\% of these patients eventually develop SNHL, and because of their lack of clinical findings at birth likely will go undiagnosed. The onset of SNHL may be immediately after birth or later in life, and the severity of the hearing loss among affected children is variable. Approximately 5\% of infants with congenital CMV infection have hearing loss at birth; another 3\% present with SNHL by age 12 months, and yet another 7\% are not identified until age 72 months.\textsuperscript{27} These findings clearly show that universal auditory screening at birth does not detect most cases of SNHL caused by congenital CMV infection. A different approach is needed in these children, perhaps CMV screening in the newborn period combined with the universal auditory screening.\textsuperscript{27}

**Antiviral Treatment**

No antiviral treatment is approved or recommended for routine use in infants with symptomatic congenital CMV infection. However, a phase III randomized study recently published by the National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group showed a benefit to ganciclovir therapy in neonates with symptomatic infection.\textsuperscript{28} This multicenter clinical trial enrolled newborns that had symptomatic congenital CMV infection with evidence of CNS involvement (microcephaly, intracranial calcifications, and neurologic abnormalities). Patients were randomized into 2 groups: treatment with intravenous ganciclovir for 6 weeks and no treatment. The findings revealed that compared with no therapy, ganciclovir protected patients from hearing deterioration up to a mean follow-up of approximately 2 years. The most common side effect in those treated patients was neutropenia.\textsuperscript{28}

The implications of these results on clinical practice remain uncertain. Questions remain regarding whether the benefit of ganciclovir therapy will be sustained over time and also regarding the long-term side effects of ganciclovir use, as the drug has the potential for carcinogenicity and reproductive toxicity and these effects are not seen until patients reach maturity.\textsuperscript{16,17} The risk of treatment side effects in infants with milder infection outweighs the benefits.\textsuperscript{17}

**PREVENTION**

Although prevention of congenital CMV infection is desirable and perhaps urgently needed, no vaccine is currently available. In the 1970s, 2 live attenuated vaccines were developed, AD-169 and Towne 125. Although initial studies with the Towne 125 vaccine were promising, its development into a useful vaccine has not occurred. Studies are needed in women of childbearing age; however, clinical trials in pregnant women are problematic owing to the fear that the attenuated vaccine virus strain could reactivate in pregnancy with the risk of being transmitted to the fetus.\textsuperscript{14,16}

Vaccines utilizing glycoprotein B as the main vaccine antigen have been developed and have shown some promise, including a recently published study demonstrating effectiveness in an animal model.\textsuperscript{29} Glycoprotein B–based anti-CMV vaccines have not yet reached the clinical trial stage, however.

While research continues on development of a vaccine, prevention is limited to identifying women at risk of CMV infection during pregnancy and counseling these women about the potential risks and measures for avoiding infection. CMV-seronegative women should be made aware of the potential for infection from close exposure to young children at home and in day care centers and advised to practice good hygiene, such as washing hands after changing diapers and avoiding sharing food or eating and drinking utensils.\textsuperscript{14,16,17}

**SUMMARY**

CMV is the most common congenital infection in the United States. Only a small percentage of infected infants are symptomatic at birth, but these infants have great potential for severe neurologic and developmental sequelae. CMV-infected infants who are asymptomatic at birth are difficult to differentiate from non-infected newborns. Ten percent to 15\% of patients in this group later present with SNHL. The diagnosis of newborns suspected of having been congenitally infected with CMV is made through obtaining a viral culture before 3 weeks of life.

There is no routinely recommended treatment for
symptomatic congenital CMV infection although some recently published studies have shown encouraging data about the use of the antiviral agent ganciclovir, and its use should be considered on an individual basis. Although several vaccines have been developed and undergone some clinical trials, none are available for clinical use at present. Prevention of infection is therefore limited to identifying women at risk of passing CMV infection to their fetuses, and advocating use of good hygienic measures.

REFERENCES