Ophthalmological Findings in Congenital Cytomegalovirus Infection: When to Screen, When to Treat?

Sofie Ghekiere, MD; Karel Allegaert, MD, PhD; Veerle Cossey, MD; Marc Van Ranst, MD, PhD; Catherine Cassiman, MD; Ingele Casteels, MD, PhD

ABSTRACT
Cytomegalovirus (CMV) is the leading cause of known congenital viral infections. Approximately 90% of congenitally infected newborns exhibit no clinical abnormalities at birth. In 5% to 15%, a wide spectrum of clinical signs is present at birth. Ophthalmological signs are seen in a large percentage of symptomatic patients but rarely in otherwise asymptomatic infants. Chorioretinitis, optic atrophy, and cortical visual impairment are the most frequent causes of visual problems in congenitally infected infants. There is no clear consensus in the literature on screening or treatment modalities concerning the ophthalmological aspects of congenital CMV. Further prospective studies are needed to set up guidelines for ophthalmological screening and treatment of infants with congenital CMV. [J Pediatr Ophthalmol Strabismus 2012;49:274-282.]

INTRODUCTION
Cytomegalovirus (CMV) is the leading cause of known congenital viral infections. The virus is a ubiquitous organism and the largest member of the herpes virus family. It consists of a double-stranded DNA core in an icosahedral capsule surrounded by amorphous material, which is in turn enclosed by a lipid envelope. The term cytomegalic inclusion disease is derived from the histopathologic feature of enlarged cells containing distinctive intranuclear inclusions.1

The overall birth prevalence of congenital CMV infection is 0.64%, but this varies considerably among different populations.2 Ninety percent of the congenitally infected infants are asymptomatic at birth, although disabilities (primary hearing loss) can appear later in life. Ten percent are symptomatic at birth (5% severe, 5% mild to moderate). Clinical manifestations of symptomatic congenital CMV include intrauterine growth retardation, thrombocytopenic purpura, microcephaly, prolonged jaundice, hepatosplenomegaly, pneumonia, intracerebral calcifications, chorioretinitis, and optic atrophy.3 Ninety percent of the infants with symptomatic congenital CMV will have significant neurological sequelae.4

We performed a literature study to highlight the ophthalmological symptoms at birth and at follow-up and to discuss the controversy on treatment options and screening modalities.

TRANSMISSION
CMV is found in all geographic locations and socioeconomic groups but is more widespread in developing countries and in communities with lower socioeconomic status. For example, the prevalence rate in Belgium is 35% to 65%, as opposed to 85% in Eastern Europe.5 The seroprevalence is also age...
dependent; 36% of individuals aged 6 to 11 years in the United States are infected with CMV compared with 91% of individuals 80 years and older.6 Thirty-five percent to 50% of pregnant women are immune to CMV. CMV is spread from one person to another by close and prolonged contact with body fluids. CMV can be found in urine, saliva, blood, feces, tears, breast milk, semen, and cervical secretions.4,7 Hand washing is effective in removing the virus from the hands.7

Newborn infection occurs as the consequence of one of four routes of transmission: intrauterine, peripartum, postnatal, and nosocomial. Intrauterine transplacental transmission is thought to occur during maternal viremia secondary to a primary infection, reinfection, or reactivation of a latent maternal infection.1,4 A recent study indicated that more children (three-quarters of congenital CMV infections) acquire congenital CMV from non-primary infection than from primary infection.8 Between 1% and 4% of seronegative women will be contaminated with CMV for the first time while they are pregnant (primary infection), and approximately 40% of those will pass on the virus to the fetus. Approximately 1% of the recurrent infections will result in a congenitally infected infant.1,4,9 Peripartal transmission may occur secondary to exposure to genital secretions at the time of delivery. Postnatal transmission may occur from ingestion of breast milk. Nosocomial infection occurs after blood transfusion or organ transplantation. Perinatal, postnatal, and nosocomial infection does not result in a congenitally affected infant.1,3,4

Trimester of exposure, maternal age, CMV serostatus, character of maternal immunity, and viral loads influence the rate of maternal–fetal transmission. Although preconception immunity to CMV was thought to provide a substantial protective effect against maternal–fetal transmission, several reports suggest that maternal antibody titers alone may not be a good indicator for fetal transmission. The qualitative aspects of the antibody response (ie, presence of neutralizing high-avidity antibodies) determine the level of fetal protection.10 IgG-virion complexes formed of high-avidity neutralizing antibodies are probably quickly neutralized by villus core macrophages on the fetal side, whereas low-avidity antibody complexes allow the virus to escape from the macrophages and infect the fetus. Both antibody avidity to CMV and the timing of infection relative to the establishment of pregnancy are critical for the level of protection of the fetus.10,11

It is well known that congenital CMV infection among infants exposed to HIV is more common than in the general newborn population, with a prevalence ranging between 2% and 7%.12 Maternal immunosuppression secondary to HIV disease can lead to reactivation of CMV. The prevalence of congenital CMV infection is also higher in infants infected with HIV than in those who are not. It could be that fetal CMV infection predisposes to fetal HIV infection rather than the opposite; CMV infection causes immunosuppression and may lead to increased susceptibility to HIV infection. Another argument is that the inflammation caused by CMV infection of the placenta results in increased numbers of HIV-infected macrophages in the placenta and a greater likelihood of transmission of HIV to the infant.13,14

**CLINICAL FINDINGS IN CONGENITAL CMV**

**Systemic Manifestations**

Clinical manifestations of symptomatic congenital CMV infection in the neonate include intrauterine growth retardation, petechial rash, thrombocytopenia, microcephaly, prolonged neonatal jaundice, hepatosplenomegaly, pneumonia, and intracerebral calcifications. Asymptomatic patients have positive urine cultures for CMV but no obvious clinical signs of disease.

Sensorineural hearing loss, mental retardation, motor disabilities, and more subtle complications can be anticipated within the first years of life in up to 90% of patients with symptomatic CMV at birth and in 5% to 15% of asymptomatic infants. Hearing problems are seen in two-thirds of symptomatic patients and in 13% of asymptomatic patients. Hearing loss has been shown to be progressive in some patients.

Microcephaly in the symptomatic group was correlated with chorioretinitis and cortical visual impairment. Cortical visual impairment was also correlated with neurodevelopmental delay.1,4

In congenital CMV, various brain abnormalities can be detected by magnetic resonance imaging, such as white matter abnormalities, cortical malformations, ventriculomegaly, and hippocampal dysplasia. The white matter abnormalities in congenital CMV are polymorphous, difficult to evaluate at a young age, and scarcely correlated with the general clinical outcome, unlike cortical malformations, ventriculomegaly, and hippocampal dysplasia.15
Ophthalmological Findings

Based on one case–control study and several case reports, we conclude that approximately 5% to 30% of infants with CMV disease have ophthalmological features. Anterior segment abnormalities include bilateral anterior polar cataract and anterior stromal corneal scars. Fundus abnormalities include chorioretinitis with or without hemorrhagic component, peripheral retinal scars, optic atrophy, and macular scars. Strabismus is a common finding in the symptomatic group. Other ocular findings are optic nerve hypoplasia, coloboma, microphthalmia, anophthalmia, and incomplete cyclopia (Table 1).

A long-term prospective study (1982–1998) of 42 symptomatic and 83 asymptomatic children with congenital CMV along with 21 control patients showed that children with symptomatic congenital CMV disease have visual impairment in 22% of the cases, compared to 1.2% of patients with asymptomatic congenital CMV. Coats et al. documented that 78% of symptomatic patients had normal vision. A moderate or severe monocular visual loss occurred in 5% of patients due to macular scars or strabismus. Severe bilateral visual impairment was due to optic atrophy or cortical blindness in 17% of patients. In the group of asymptomatic patients, 98.8% had normal vision. Moderate visual loss was due to a macular scar in 1.2% of patients. No patients in this group had severe visual loss.

Optic atrophy and cerebral visual impairment are thought to be due to a direct infiltration of the central nervous system, the optic nerves, or both by the virus early in the first trimester of the pregnancy. CMV chorioretinitis was thought to be rarely progressive postnatally and as such different from toxoplasmosis. A series of 7 patients with progressive chorioretinitis suggest that there is either progression of an existing retinal lesion or a delayed development of chorioretinitis after the first year of life in 23% of patients with congenital CMV with chorioretinitis. The age of reactivation or delayed onset was between 1 and 10 years. There was no correlation between the progression of chorioretinitis and newborn findings including jaundice, hepatosplenomegaly, microcephaly, thrombocytopenia, and elevated alanine aminotransferase. There was also no correlation between retinal disease progression and sequelae of congenital CMV. There was no evidence of systemic viral replication or systemic reactivation at the time of delayed onset or progression as suggested by negative urine cultures for CMV in all but one, negative blood cultures, and the absence of a significant fluctuation in the concentration of antibodies against the major envelope glycoprotein of CMV, gB.

DIAGNOSIS

Diagnosis of congenital CMV infection is made by detection of CMV in the tissues, saliva, or urine of the infant within the first 3 weeks of life. Urine is usually tested because it contains the highest concentration of the virus. The definitive diagnosis of congenital CMV is made by isolation of the virus in urine by viral culture or by detection of CMV DNA in urine and/or blood via polymerase chain reaction (PCR). Quantitative PCR testing for CMV also allows monitoring of the viral load of patients infected with CMV. Neonatal IgM is not a reliable marker for congenital CMV. The IgM prevalence of congenitally infected infants is only 20% to 40%.

To screen newborns for a variety of metabolic and endocrine disorders, dried blood spots are collected within 7 days after birth on filter paper (Guthrie cards). In a population-based study performed in California, Khazarri et al. tested dried blood spots by PCR for cytomegalovirus DNA. Prevalence of congenital CMV was almost identical to that found in other studies using methodology of virus culture of urine. Specificity of CMV PCR assays on dried blood spots has been reported to range between 99.3% and 100%. But CMV testing based on dried blood spots likely has lower testing sensitivity than urine- or saliva-based testing because CMV viral load is significantly lower in blood than in urine or saliva. Numerous studies have reported a correlation between higher CMV viral load in newborns and the presence of sequelae. Thus, the clinical sensitivity of a dried blood spots test, based on the detection of children who will eventually develop sequelae, is high. CMV PCR of neonatal blood stored on Guthrie cards seems to be a promising test for newborn screening and can help, even years after birth, to diagnose congenital CMV in children with visual or hearing impairment of unknown cause.

Rozanova et al. investigated the level of specific anti-CMV antibodies in tears in patients with CMV retinitis. There was a strong association between high tear levels of anti-CMV antibodies and active ocular infection. Eighty percent of children with congenital CMV infection and chorioretinitis were positive...
for specific anti-CMV antibodies in tear fluid, in contrast to only 5% of the control group. This finding suggests that there is a local deposition of CMV antibodies in tears in children with congenital CMV infection and chorioretinitis, independent from the level of antibodies in the serum. These anti-CMV antibodies in tears can be used as a marker for active ocular CMV infection.26

**VACCINATION**

In various clinical trials, different CMV vaccine candidates have been tested. The most encouraging results to date have been observed in studies of a vaccine based on the immunodominant envelope glycoprotein B (gB): the gB/MF59-vaccine. A randomized double-blind, placebo-controlled clinical trial in seronegative women showed an overall efficacy of 50% in preventing CMV infection.27 There is pending evidence that non-primary maternal infections account for more of the disease burden associated with congenital CMV infection than generally presumed.8 This generates a rationale for vaccinating women of childbearing age who are already CMV seropositive. More studies on the efficacy of gB/MF59 vaccine to prevent CMV reinfection in seropositive women seem to be warranted.27

### TREATMENT OF SYMPTOMATIC CONGENITAL CMV

Ganciclovir and valganciclovir are the only two medications that have been employed in the treatment of congenital CMV infection to date. Both...
have to be phosphorylated by UL97, a kinase unique to CMV replication, and they competitively inhibit the incorporation of deoxyguanosine triphosphate into elongating viral DNA.\textsuperscript{28}

A study of Nigro et al. compared two regimens of ganciclovir treatment (5 mg/kg twice daily for 2 weeks versus 7.5 mg/kg twice daily for 2 weeks followed by 10 mg/kg three times a week for 3 months) within the first 2 weeks of life in two small groups of neonates with congenital CMV with central nervous system manifestations. In all infants, viral shedding reappeared after discontinuation of treatment. Normal neurological development at 18 months was noted in 2 of 6 patients in the first group and 4 of 6 patients in the second group. No side effects were reported in the first treatment group. Side effects with the higher-dose, longer-duration regimen were neutropenia, elevated liver enzymes, and difficulties for venous access.\textsuperscript{29}

A larger phase II study compared two 6-week regimens (8 mg/kg/day versus 12 mg/kg/day) in patients with symptomatic congenital CMV. The group receiving 12 mg/kg/day (28 infants) showed a more pronounced antiviral effect in urine compared with the lower dose group (14 infants). In all children, viral shedding in urine reappeared after discontinuation of therapy. Of 14 children with retinitis at baseline, 8 had complete normalization at 6 months. Three infants developed retinal detachment. It was not specified whether retinopathy of prematurity was involved. Of the children with normal ophthalmological evaluation at baseline, 3 developed retinal scarring attributed to CMV.\textsuperscript{4,30}

The only case–control study of ganciclovir therapy in children with symptomatic congenital CMV disease to date was conducted by the National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. In this phase III study, 100 neonates younger than 1 month of age were enrolled to receive intravenous ganciclovir (6 mg/kg/dose every 12 hours for 6 weeks) or no treatment. All children had one or more consequences on the central nervous system: microcephaly, intracranial calcifications, chorioretinitis, impaired hearing, and abnormal cerebrospinal fluid. Functional evaluation at 6 months and 1 year showed significantly less hearing deterioration ($P < .01$) in treated infants (0% and 21%, respectively) compared to non-treated infants (41% and 68%, respectively). Neutropenia occurred more frequently (63%) in the treated group than in the control patients (21%).\textsuperscript{4,31} The Denver Developmental Tests were used to score the developmental delay in the same group of infants. Infants with symptomatic congenital CMV involving the central nervous system receiving intravenous ganciclovir had fewer developmental delays at 6 ($P < .02$) and 12 ($P < .07$) months compared with untreated infants. But the large proportion of unevaluable patients raises concerns about follow-up bias and the strength of both conclusions.\textsuperscript{4,32}

Tanaka-Kitajima et al. used real-time PCR to monitor the viral load in six cases of symptomatic CMV infection that received ganciclovir at a dose of 5 to 12 mg/kg/day for 2 to 7 weeks.\textsuperscript{21} Ganciclovir transiently suppresses the concentration of CMV. Subsequent increases of viral titers do not appear to be correlated with the clinical course or neurological outcome.

The use of ganciclovir was limited to children with symptomatic disease because ganciclovir induces hematological abnormalities, especially neutropenia, and catheter-related problems. Animal experiments showed that high-dose treatment induces testicular damage, affects sperm variables, and may have carcinogenic effects.\textsuperscript{4,28-30}

Kimberlin et al. assessed the pharmacokinetics of valganciclovir, the oral prodrug of ganciclovir, and found that a dose of 6 mg/kg intravenous ganciclovir and 16 mg/kg oral valganciclovir provides similar systemic exposures to ganciclovir.\textsuperscript{33,34} The toxicity of valganciclovir is similar to ganciclovir, with 38% of subjects developing mild to moderate neutropenia.

Data on the use of antiviral agents other than ganciclovir for CMV infection in the neonatal period are limited. The concurrent use of ganciclovir and foscarnet treatment for CMV encephalitis and retinitis was described in an infant with acquired immunodeficiency syndrome. Cidofovir has been used in an infant with severe combined immunodeficiency disease that acquired CMV perinatally. More research is definitely needed on the use of cidofovir and foscarnet for congenital CMV. New developments such as Maribavir (Viropharma, Exton, PA) are underway. Maribavir is a compound in the halogenated benzimidazole family and inhibits CMV replication by targeting the viral enzyme terminase. Because it does not have to be phosphorylated by UL97 kinase, as does ganciclovir, it has potential to be useful in the treatment of ganciclovir-resistant
strains of CMV. Until now, Maribavir has exhibited promising safety (without nephrotoxicity or hematological toxicity) and pharmacokinetic properties in adult volunteers.35

**TREATMENT AND THE EFFECT ON RETINITIS**

Table 2 provides an overview of the different case reports and case series published in the past 25 years.

Nigro et al. compared two regimens of ganciclovir treatment within the first 2 weeks of life in two small groups of neonates with congenital CMV with central nervous system manifestations.29 In the first group, 3 patients had chorioretinitis that did not change with treatment. In the higher-dose, longer-duration treatment group, resolution of the chorioretinitis was found in 2 patients.

Whitley et al. used 4 or 6 mg/kg/dose twice a day for 6 weeks to treat 14 children with retinitis.30 Resolution of retinitis occurred in 8 children. Six children suffered from retinal detachment, optic atrophy, or retinal hemorrhage.

Baumal et al. studied 9 immunocompromised children with CMV retinitis, one of whom had congenital CMV.36 Five children received intravenous ganciclovir (5 mg/kg twice daily) and 4 children received foscarnet (60 mg/kg three times daily). After 4 weeks of treatment with intravenous ganciclovir, a complete regression of chorioretinitis was noticed in a child with congenital CMV.

Coats et al. found only 1 of 125 children with (a)symptomatic congenital CMV had active chorioretinitis.1 The lesions in this child with symptomatic CMV presented as full-thickness retinitis without hemorrhages outside the major vascular arcades and were randomly distributed. Most of the lesions progressed in size over a period of several weeks and new lesions appeared. Treatment with ganciclovir (dose unknown) was initialized and resulted in dra-
matic and rapid resolution of the active retinitis and overall improvement of the patient’s systemic problems. The lesions remained inactive during almost 2 years of follow-up.

Noffke et al. reported the case of a female infant with symptomatic congenital CMV and bilateral intra-retinal hemorrhages 1 week postnatally.37 Five weeks later, multiple perivascular areas of retinitis developed. The child received no treatment because of the potential toxicity of ganciclovir and the otherwise stable condition of the child. The retinitis resolved within 3 weeks and remained inactive during the next 6 months.

The case of a 9-day-old infant with symptomatic congenital CMV and active progressive bilateral CMV retinitis was discussed by Barampouti et al.38 Because the vasculitis progressed and involved the macula in one eye, treatment with ganciclovir 5 mg/kg/day was started. Dramatic improvement of the retinitis occurred within 1 week of treatment and ganciclovir was stopped after 3 weeks.

As described above, Kimberlin et al. evaluated the efficacy of 6 weeks of ganciclovir (6 mg/kg/dose twice a day) versus no treatment.31 There was no statistically significant difference in time to resolution of CMV retinitis between the treatment groups, although only 8 patients had retinitis at baseline.

Weng et al. described a female neonate with symptomatic congenital CMV infection and retinitis in both eyes.39 Therapy with ganciclovir at 5 mg/kg/day every 8 hours for 3 weeks was started intravenously. Human anti-CMV immunoglobulin (misoprostol) was given at 400 mg/kg every other day for 10 doses. A month after initiation of treatment, the retinitis had disappeared.

A 2-month-old female infant with a hypopigmented lesion one-fourth disc in diameter along the temporal arcade in the right eye was studied by Brubaker et al.20 The lesion in the right eye had progressed to several punched-out chorioretinal lesions in the right macula within 1 month. In the left eye, increased granularity was seen in the macula and several hypopigmented lesions in the midperiphery were present with white-feathered vitreous changes. Active CMV infection was confirmed by urine culture and PCR detection of CMV DNA in the blood. Because of this progressive CMV retinitis, the child was treated with intravenous ganciclovir 5 mg/kg/day for 6 weeks. After this treatment, the lesions were less active but not fully resolved with a persistent granular salt-and-pepper appearance.

Shoji et al. described a 7-day-old infant with symptomatic congenital CMV and bilateral active chorioretinitis that triggered a 6-week treatment with intravenous ganciclovir (12 mg/kg/day every 12 hours).40 Two weeks after discontinuation of therapy, chorioretinitis partially recurred and ganciclovir therapy with the same dose was reinitiated. After 9 weeks of therapy, the treatment was changed to oral valganciclovir (32 mg/kg/day every 12 hours) because of incomplete stabilization of chorioretinitis under intravenous therapy. Oral valganciclovir was continued for 7 weeks. His ophthalmological condition remained stable without active lesions 1 year after the completion of antiviral therapy.

The major toxicity in patients receiving ganciclovir is hematologic, notably neutropenia. However, the incidence of neutropenia in infants infected with congenital CMV varies significantly. In the clinical trial conducted by Kimberlin et al., neutropenia developed in 63% of infants with congenital CMV infection who received ganciclovir during the first 6 weeks of treatment.31 However, Tanaka-Kita-jima et al. reported that neutropenia did not develop in any of 6 Japanese cases of congenital CMV during ganciclovir treatment.21 Similarly, Nigro et al. found neutropenia only in 1 of 12 cases of congenital CMV treated with ganciclovir.29 It would be useful to identify any indicator, especially host factors, predictive of neutropenia in ganciclovir therapy.

**DISCUSSION**

CMV is the most common cause of congenital viral infection in humans, affecting approximately 0.64% of all live births.2 A variety of clinical ophthalmological signs are associated with congenital CMV, such as optic atrophy, macular scars, strabismus, cortical visual impairment, and chorioretinitis. To allow for early intervention, patients with congenital CMV should have repeated eye examinations.41 Screening for congenital CMV is currently not recommended. To detect congenital CMV, a urine culture and PCR on urine or blood can be performed if a maternal CMV infection is diagnosed during pregnancy or if a prenatal ultrasound presumes a congenital CMV infection. A diagnosis of primary maternal CMV infection during pregnancy is documented by either seroconversion or detection of specific IgM antibody associated with low-avidity IgG. A recurrent infection can be diagnosed by an increase of IgG antibodies (of high avidity) with or
without detectable IgM antibodies. Because of the high prevalence of congenital CMV and the resulting disease burden, a universal screening test seems necessary. CMV DNA detection in dried blood spots is technically feasible, but DNA extraction protocols still have to be optimized before it can be used as a screening tool. The ophthalmological screening in patients with congenital CMV, consisting of biomicroscopy and a dilated fundus examination, should be performed after birth, at 6 months of age, and then annually during the first 10 to 12 years of life. We know that chorioretinitis can be progressive and present later in life. With these repeated fundus examinations, late-onset and progressive chorioretinitis can be detected and treated. The association of strabismus, amblyopia, and cerebral visual impairment with congenital CMV is another argument for continued ophthalmological examination with a measurement of the visual function as soon as possible.

To date, there is no large prospective clinical trial about the effect of antiviral therapy for active chorioretinitis. There are only a few case reports and case series in the literature describing clinical outcomes in patients after treatment with ganciclovir. The results of these cases are not straightforward: some reports showed resolution of CMV retinitis after ganciclovir treatment in symptomatic congenital CMV, others demonstrated no treatment benefit. A few reports demonstrated that longer duration of therapy up to 3 months was necessary to control chorioretinitis.

There are no data on treatment of children with congenital CMV without central nervous system manifestations, except for 4 patients treated for severe CMV pneumopathy. However, patients with asymptomatic congenital CMV at birth can develop ophthalmological signs; there is an incidence of chorioretinitis in up to 1% of asymptomatic patients.

To investigate the benefit (and the possible harm) of antiviral treatment in patients with symptomatic congenital CMV, a clinical trial should be set up. In a large prospective longitudinal study, different treatment regimens could be compared for their effect on vision and on chorioretinitis. In our opinion, treatment with ganciclovir for ophthalmological manifestations of congenital CMV should be considered for chorioretinitis in symptomatic children (ganciclovir 6 mg/kg/dose intravenously every 12 hours) and chorioretinitis spreading to the posterior pole in asymptomatic children (ganciclovir 6 mg/kg/dose intravenously every 12 hours). The potential benefit of treatment should be weighed against the potential risk of neutropenia and gonadal toxicity or carcinogenicity. There is an urgent need for prospective clinical trials concerning the screening and treatment of patients with congenital CMV. To date, weighing the harm and benefits of treatment is necessary for each individual patient.

REFERENCES

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