

Cytomegalic inclusion disease of the newborn- A short review

Prashant Mule¹, Sanjeev H^{2,*}, K. Sneha³, Abhay Kumar⁴

^{1,3,4}Consultant, ²Associate Professor, Dept. of Microbiology, Andaman and Nicobar Islands Institute of Medical Sciences, GB Pant Hospital, Andaman and Nicobar Island, Port Blair, India

***Corresponding Author:**

Email: drsanjeevh@gmail.com

Abstract

CMV infection is common in all populations but rarely associated with symptomatic illness in immunocompetent individuals. Immunocompromised patients are more commonly affected and it is a major cause of multi-organ dysfunction. The severity of disease depends upon degree of immunosuppression. Infection with CMV is extremely common but disease is a rare occurrence. The large majority of infections are clinically inapparent as with other Herpes virus infections, leading to prolonged latency, with occasional reactivation. Intrauterine or postnatal infections may lead to the development of clinical disease. Cytomegalic inclusion disease is seen almost exclusively in infants born to mothers developing primary CMV infection during pregnancy. Cytomegalic inclusion disease of the newborn or fetal death are common sequelae of Intrauterine CMV infections. This is associated with hepatosplenomegaly, jaundice, thrombocytopenic purpura and hemolytic anemia. The cytomegalic inclusion disease is probably the most important cause of microcephaly. Other manifestations are chorioretinitis and cerebral calcification. Survivors may show mental retardation. The diagnosis of CMV relies on demonstration of the agent (virus, viral proteins and nucleic acids) either in body fluids, and/or tissue or on serological responses in a patient with clinical findings consistent with CMV infection. Antivirals for systemic treatment of congenital and perinatal CMV infection are ganciclovir and valganciclovir. High-risk group such as patients undergoing allogeneic bone marrow organ transplantation, acquired or innate immunodeficiency syndromes and premature infants are ideal candidates for prophylaxis against CMV infection. Administration of CMV immunoglobulins and screening of blood and organ donors for virus and its products are considered in prevention.

Keywords: Multi-organ dysfunction, Microcephaly, Chorioretinitis, Ganciclovir.

Introduction

Cytomegaloviruses (CMVs) formerly known as salivary gland viruses are double stranded DNA viruses belong to the family of herpesviridae and subfamily beta-herpesviruses. Being 150-200 nm in size, CMV are the largest in the herpesvirus family. Cytomegaloviruses can be grown in human fibroblast cultures. Epithelial cell cultures are not susceptible though epithelial cells are affected in vivo. As the cytopathic effects of CMV are slow in appearance, cultures have to be incubated for up to 50 days. CMV virus is highly species specific that infects many animals including human's especially immunocompromised patients.¹ The most characteristic feature is enlargement of infected cells and prominent intra-nuclear inclusions. Good pasture and Talbot (1921) used the term 'Cytomegalic' for cell enlargement in CMV infections. In 1956, the virus was isolated from human sources independently by Smith, Rowe and Weller. Weller proposed the name 'cytomegalovirus' for this group of viruses in 1960. Whenever hosts immunity is compromised,² CMV undergoes periods of reactivation and periods latency as like other herpesviruses. The virus remains in the host's body indefinitely and can reactivate at any point of time depending on immune status. More than 80% of population in the developing world demonstrate CMV IgG antibodies, as infection with CMV is very common. The mode of transmission is via the trans-placental route. The chances of severe malformations (MF) and prognosis depends on gestational age of the fetus. The

maternal infection can either be primary (in women who had never been infected before) or recurrent (by viral reactivation or reinfection by other viral strains).³ The frequency of severe complications are greater when the infection is primary as the chances of transmission to the fetus are higher. In the United States and Western Europe, CMV is a leading cause of congenital infection leading infectious cause of brain disease and hearing loss in children.

The apparent clinical disease develops in ten percent of infected newborns (NB). Infected newborns may suffer serious sequelae following infection and mortality rate may be as high as 30% to 90%⁴.

Clinical Manifestations of Congenital CMV Infection

The clinical features of symptomatic CMV infections are jaundice, hepatosplenomegaly, microcephaly, intrauterine growth retardation (IUGR), prematurity, cerebral calcifications and chorioretinitis.⁵ Delayed clinical manifestations such as deafness, mental retardation that can all appear during the first two years of life in 10 to 15% of the newborns.^{6,7} Asymptomatic congenital CMV infection is defined as the presence of CMV in any secretions within the first 3 weeks of life, but with normal clinical, laboratory and radiological examinations and only about 7 to 10% have clinically evident disease at birth.⁸ The majority of infants born with congenital CMV infection are asymptomatic at birth. The classical triad on congenital CMV infection is constituted by jaundice (62%), petechiae (58%), and

hepatosplenomegaly (50%).⁹ Other clinical manifestations include sensorineural hearing loss, oligohydramnios and polyhydramnios, prematurity, non-immune hydrops, fetal ascites, hypotonia, poor feeding, lethargy, thermal instability, cerebral ventriculomegaly, “blueberry muffin” spots and, less frequently, hepatitis, pneumonia, osteitis, and intracranial hemorrhage.^{10,11}

Approximately two-thirds of infants born with symptomatic congenital CMV infection shows intracranial calcifications. Infants with symptomatic CMV infection may be at increased risk for the presence of congenital malformations such as inguinal hernia in males, high-arched palate, hydrocephalus, clasp thumb deformity, and clubfoot.^{12,13}

Table 1: Clinical presentation of congenital CMV infections

General Findings	CNS Manifestations	Radiological Findings
Prematurity	Chorioretinitis	Pneumonia
Jaundice	Microcephaly	Periventricular, thalamic and cortical calcifications
IUGR	Seizures	Cortical dysplasia
Purpura, petechiae	Hypotonia	Ventriculomegaly
Hepatosplenomegaly	Hearing impairment	-
Nonimmune hydrops fetalis	-	-
Blueberry muffin spots	-	-

Congenital CMV infection needs to be evaluated very carefully for malformations. The average mortality for symptomatic congenital CMV infections is 7-10% but many researchers have reported mortality rate as high as 30%. Non-cerebral manifestations of the infection, such as hepatic dysfunction or bleeding are common causes of death.¹⁴

Predisposing factors for congenital CMV infection

Study from Department of Pediatrics, University of Alabama, USA reported significant associations between congenital CMV infection and caring for preschool children in the year before delivery, onset of sexual activity < 2 years before delivery, sexually transmitted diseases during pregnancy, household size > 3 people, and maternal age < 25 years were identified as independent risk factors.¹⁵ Preece *et al.* compared the mothers of a group of congenitally infected infants with those of the screened population of women with non-infected infants.¹⁶ The age of the mother, race and marital status were all individually strongly associated with the prevalence of congenital CMV infection. The overall rate of congenital CMV infection was 3/1000 live births, but it ranged from 25/1000 for single black women under 20 years old to 1-6/1000 in married or cohabiting white women over 25 years of age. A study conducted by Marianne A.B. et al in Gambia in 2007 reported the prevalence of congenital CMV among healthy neonates was much higher than previously reported in industrialized countries, and was associated with active placental malaria infection. There were no obvious clinical implications during the first year of life.¹⁷

Modes of Transmission

Transmission of CMV occurs from person to person through body fluids, and requires close contact with contaminated secretions because the virus is not very

contagious. CMV can be found in blood, urine, semen, cervical secretions, saliva, breast milk and transplanted organs, all these sites intermittently excrete viruses.^{18,19} CMV spreads slowly and probably requires close contact for transmission. It may spread through salivary or other secretions or by sexual contact. A special method of transmission is by blood transfusion or organ transplants. Congenitally infected infants have viremia for upto 4-5 years. They are highly infectious in early infancy. After primary infection, viral excretion is prolonged over years but also occurs with reactivation of latent infection.²⁰ Transmission of CMV to fetuses and newborn infants occurs in one of following ways: (1) in utero by transplacental passage from hematogenous spread to the fetus during maternal viremia; (2) at birth by intrapartum passage after exposure to infected cervical and vaginal secretions; (3) postnatally by ingestion of CMV positive breast milk or infected blood transfusion.²¹⁻²³ Infected breast milk is an even more efficient source of early-acquired infection. Virus has been isolated from breast milk in a substantial proportion of seropositive women. Hayes *et al.* isolated virus from milk or colostrum from 17 of 63 (27%) seropositive women and virus was isolated significantly more often after the first week than before.²⁴ Stango *et al.* similarly reported high rates of isolation. In a population with a high sero-positivity rate, transmission through breast milk is likely to be a major source of early infection.

Epidemiology

Examining the sources of virus, identifying populations at risk and defining patients with deficits in immunity will better help us to understand the epidemiology of CMV infections. CMV can be cultured from most body fluids for extended periods following primary infection with significant amounts of infectious virus being found in urine, genital secretions (including semen), saliva, and breast milk. Congenital CMV

infection is the most common viral infection of the human fetus. In the USA, the incidence of congenital CMV infection is 1 percent in live births.²⁵ In the developing countries, the rate may be much higher. Up to 80 per cent of adults show CMV antibodies, indicating the high prevalence of infection. Once infected, the person carries the virus for life. In the developing world, rates of congenital infections as high as 2-3%, suggesting that immunity does not prevent intrauterine infection.¹¹ An estimated 10 percent of infected infants will have significant infections that result in long lasting CNS sequelae. Primary gestational infection with CMV results in a 35-50 percent fetal transmission rate, whereas gestational reactivation or reinfection in women with pre-conceptual immunity is associated with a fetal infection rate of between 1-3%. Fetal infection following primary maternal infection during pregnancy results in damage three times more often than infection that follows reactivation or reinfection in women with pre-conceptual immunity. These data include the finding that maternal reinfections with a genetically different strain of CMV do occur at a significant rate (10-12%) and that maternal reinfections can lead to damaging congenital infection.²⁶ Many authors reported congenital infections following non-primary maternal infections could result in a similar incidence of long-term sequelae as observed in infants infected because of primary maternal infections during pregnancy. Naturally, acquired intrapartum or postnatal CMV infection in normal newborn infants has not been associated with severe infections and the permanent sequelae characteristic of infants infected in utero.

Discussion

Infection with CMV is common in all human populations and infrequently associated with symptomatic illness in normal hosts. In contrast, it is a major cause of multi-organ disease in immunocompromised patients, the severity of disease being related to the degree of immunosuppression. The role of latent infection in the transmission of CMVs by blood or during allograft transplantation is well accepted; however, the importance of latent versus a persistent productive infection in the maintenance of the virus in the individual and a population remains unclear. Human CMV can be found in tissue from a variety of inflammatory and neoplastic diseases, raising the possibility that this virus may directly or indirectly contribute to chronic inflammatory disease and cancer. Three groups of patients are at risk for invasive acute CMV disease: (1) newborn infants infected in utero, (2) immunocompromised allograft recipients (bone marrow and solid organ transplantations) and (3) patients with advanced AIDS with CD4 lymphocyte count less than 500 cells/mm³. Infants infected in utero may be born with subclinical infections or may have a constellation of clinical abnormalities characteristic of what has been termed cytomegalic inclusion disease (CID) of the

newborn.²⁷ Cytomegalovirus disease is rare but infection with the virus is extremely common. As with herpes simplex the large majority of infections are in-apparent, leading to prolonged latency, with occasional reactivation. Clinical disease may be caused by either intrauterine or postnatal infections. Intrauterine infection leads to fetal death or cytomegalic inclusion disease of the newborn which is often fatal. This is a generalized infection associated with hepatosplenomegaly, jaundice, thrombocytopenic purpura and hemolytic anemia. The cytomegalic inclusion disease is probably the most important cause of microcephaly. Other manifestations include chorioretinitis and cerebral calcification resembling congenital toxoplasmosis. Survivors may show mental retardation. Cytomegalic inclusion disease is seen almost exclusively in infants born to mothers developing primary CMV infection during pregnancy. Infants of mothers who have CMV reactivation during pregnancy tend to have chronic subclinical infection. Perinatal infection may be acquired from the infected mother through genital secretions or breast milk. Clinical findings include hepatosplenomegaly, jaundice, thrombocytopenia, purpura, microcephaly, chorioretinitis and, rarely, pneumonia in approximately 10 percent of congenitally infected.^{28,29} Mortality rates range from 11 to 20 percent in symptomatic infection, and up to 50 percent of long-term survivors of symptomatic infections will have deficits in perceptual and cognitive functions.^{30,31}

A significant number of infants with asymptomatic infections are also at risk of developmental abnormalities, hearing loss being the most common.³²⁻³⁴ Persistent infection with prolonged viral shedding is nearly universal in infants with either symptomatic or asymptomatic congenital infection.³⁵ Congenital CMV infections are currently the most common intrauterine infections worldwide, with a prevalence of 0.2 to 2.2%. They are the primary infectious cause of malformations of the central nervous system (CNS) and the principal cause of deafness and learning difficulties in childhood and have a major social impact.^{36,37} A study in Finland detected a prevalence of congenital CMV infection of 4.8% among premature newborns, below 34 weeks, at a neonatal ICU, with full term NB not enrolled on the study.³⁸ In Milan, Italy, the observed prevalence among the general population of a neonatal ICU was 1%.³⁹ A study conducted by Santos et al. in Minas Gerais found a prevalence of congenital CMV infection at an ICU neonatal of 6.8%.⁴⁰ In a neonatal ICU in Japan a prevalence of 10% of congenital CMV infection was observed. Babies who tested positive were premature. In selected populations, such as newborn infants in neonatal intensive care units (NICU), this prevalence can climb even higher, primarily because critically ill newborns are likely to have the same risk factors. Several different studies associate adolescent mothers, black race, sexual activity with multiple partners, single marital status, multiparity, low socioeconomic status and

contact with sources of CMV (at daycare, for example) with increased risk of congenital infection.⁴¹ A number of studies performed in Brazil have observed prevalence rates that vary, depending on study population, from 0.39 to 6.8%.^{42,43} Over a five-year period study of Kazimiera Gajl-Peczalska et al, from the Laboratory of Morbid Anatomy, Szpital Dzieciacy, Saska Kepa, Warsaw, Poland observed 20 cases of generalized cytomegalic inclusion disease, which amounts to 5% of all necropsies

and 6.4% of necropsies in infants under 1 year of age, and all these children died between the second and the sixth month of life. The following criteria for differentiating the congenital and postnatal forms of the condition in infants are suggested. These criteria for differentiating the neonatal and postnatal form of the condition are suggested on the basis of clinical manifestations and necropsy findings.

Table 2: Differentiating features of cytomegalic inclusion disease of Congenital Neonatal and Post-neonatal Form

Neonatal Period	Congenital Neonatal Form	Post-neonatal Form
Age	Under 3 months	Over 3 months
Clinical Features	a) Characteristic severe form including jaundice, hepatosplenomegaly, and thrombocytopenic purpura, or first manifestations connected with infection observed during first 4 weeks of life. b) Presence of cerebral manifestations.	a) Presence of another severe primary illness, e.g. fibrocystic disease of pancreas or Werdnig-Hoffman syndrome. b) Lack of cerebral manifestations.
Necropsy Findings	a) Interstitial inflammation present in several viscera, cytomegalic cells, degenerating or containing intranuclear as well as cytoplasmic inclusion. b) Salivary glands not involved or involved with same intensity as other glands.	a) Lack of interstitial inflammation, cytomegalic cells well preserved, containing mainly intranuclear inclusions. b) Most intense changes in salivary glands.

Adapted from Kazimiera gajl-peczalska et al, Cytomegalic Inclusion Disease* Laboratory of Morbid Anatomy, Szpital Dzieciacy, Saska Kepa, Warsaw, Poland, Arch. Dis. Childh., 1967, 42, 14.

Kazimiera gajl-peczalska et al, reported and discussed 20 cases of generalized cytomegalic inclusion disease in infants 2-6 months of age. Generalized cytomegalic inclusion disease was found in 5% of unselected necropsies from the laboratory of morbid anatomy of a Warsaw Children's Hospital. This apparently high figure is probably related to the rather detailed microscopical examination undertaken, since the cytomegalic cells in the investigated organs were most frequently single. Moreover, in 17 of the 20 cases other changes were found, which might have been the cause of death. The rapid acquisition of CMV infection in the first months of life in children of seropositive mothers, and its relative absence among infants of seronegative mothers suggests that the mother is the major source of infection. Of 253 infants screened at birth to exclude congenital CMV, and followed up three-monthly for one year, 12% had acquired infection by three months and 20% by one year. In all children the infection was subclinical. The mother's serological status and whether the infant was breast fed were the major factors determining the risk of acquiring infection⁴⁴. Thirteen of the infected infants were re-examined at three years and all were still shedding virus in their urine. This demonstrates that virus shedding persists for years

in those that acquire infection early. Unless CMV is detected in the urine within three weeks of birth, congenital and acquired infection cannot be distinguished, even when clinical problems suggestive of congenital infection are present.

Diagnosis

The diagnosis of CMV infection or symptomatic disease relies either on demonstration of the agent (virus, viral proteins and nucleic acids) in body fluids and tissue. Serological screening can be employed in a patient with clinical findings consistent with CMV infection. Diagnosis may be established by recovery of the virus from the urine, saliva or other body fluids by inoculating human fibroblast cultures. A simpler but less reliable technique is the demonstration of cytomegalic cells in the centrifuged deposits from urine or saliva. Antibody demonstration is useful in the diagnosis of primary infection but not in reactivation. Serological techniques in use include complement fixation (CF) test, immunofluorescence and ELISA. Antibody detection may be necessary for screening blood or organ donors. Because of the ubiquitous nature of CMV, it is important that a distinction be made between the detection of CMV and demonstration of CMV in the context of an

infectious syndrome compatible with CMV. Multiple methods of recovering virus have been employed, including culture on permissive cells such as primary human fibroblasts and centrifugation enhanced culture followed by early antigen detection with monoclonal antibodies. This latter technique is widely used and can provide positive results within 24 h. In contrast, conventional tube culture may require up to 4 weeks to reveal cytopathology.⁴⁵ Congenital CMV infection has traditionally been diagnosed in the neonate via one of the following ways: (1) positive CMV culture of body fluids, (2) the presence of CMV specific immunoglobulin M titers in the infant's serum, or (3) demonstration of large intra-nuclear inclusions with small variable

intracytoplasmic inclusions in CMV infected visceral cells. The molecular techniques like PCR are highly sensitive and specific and offer more accurate and reliable results with less turnaround time from direct clinical specimens. Molecular tests appears to be the most reliable means for diagnosing the infection in newborns.⁴⁶ Neto et al. demonstrated in 2004 Guthrie test results from many regions in Brazil produced using ELISA-IgM serology for CMV from 15,873 newborns. Thirty-nine of them had IgM tests that were positive for CMV (0.2%). These newborns and their mothers were retested and just 16 (0.1% of the total) had the result confirmed.⁴⁷

Table 3: Diagnostic modalities for CMV in different group of patients

Type of patient	Diagnostic modality	Remarks
Maternal infection	IgG seroconversion (appearance of virus-specific IgG in the serum of a pregnant woman who was previously seronegative) Presence of anti-CMV IgM and IgG antibodies Anti-CMV IgG avidity test	Two consecutive maternal blood samples need to be collected 2-3 weeks apart. IgM can be detected in: reactivations or reinfections; until more than one year after CMV primary infection; interference due to rheumatoid factor of the IgM class or cellular antigen; false positive during other viral infections (B19 Virus, Epstein Barr Virus, etc.). Low avidity means recent maternal infection, but threshold differs between virological methods.
Fetal infection	Amniocentesis to assess the presence of CMV by PCR	Perform the test after the 21st week of gestation and after 5-6 weeks from the estimated onset of infection. Indications are: woman with compatible clinical signs of primary CMV infection; compatible ultrasound abnormalities; serologic suspicion of a recent maternal infection.
Neonatal infection	Culture or CMV-DNA testing by PCR in urine, blood, throat and CSF.	If infection is confirmed, classify as symptomatic or asymptomatic and follow-up at 1, 3, 6 and 12 months and annually until school age in order to detect sequelae with delayed onset.

Aadapted from Coll O, Benoist G, Yille Y, Weisman LE, Botet F, Anceschi MM, Greenough A, Gibbs RS, Carbonell-Estrany X, Wapm; Perinatal infections working group. Guidelines on CMV congenital infections. J Perinat med 2009; 37: 433-445.

Early diagnosis of CMV infection reduces morbidity and mortality provides a scope for early therapeutic interventions. Determining the risk of future complications in asymptomatic newborns possess great challenge.⁴⁸

Treatment

Ganciclovir and valganciclovir, which is an oral prodrug of ganciclovir, are commonly used for systemic treatment of congenital and perinatal CMV infection. Cidofovir and Fomivirsen are two additional drugs licensed for treatment of CMV infections in AIDS patients especially CMV retinitis. In a randomized controlled, multicenter, phase III study with ganciclovir

(6 mg/kg/dose intravenously every 12 hour for a 6 week course) was carried out to treat newborn infants who have congenital CMV infection involving the CNS, as defined by microcephaly, intracranial calcification, abnormal findings of cerebrospinal fluid, chorioretinitis and/ or hearing deficit⁴⁹. When tested at 6 months, 84% of treated infants maintained normal hearing or improved their hearing, in contrast to 59% of control infants. At 6 months follow-up, none of the treated infants had hearing deterioration, while 41% of control patients did. Pharmacokinetic and pharmacodynamic study of oral valgancyclovir in treatment of infants with congenital CMV infection, it showed that a 6 mg/kg intravenous ganciclovir dose and 16 mg/kg oral

valganciclovir provides similar systemic exposure to ganciclovir. Toxicity of valganciclovir is similar to that of ganciclovir with 38% of subject's developing neutropenia. A six weeks treatment with ganciclovir for

symptomatic infants with congenital CMV infection involving the CNS may be considered but cannot be recommended routinely.

Table 4: Treatment of congenital CMV infection

Antiviral Agents	Dosage/Duration	Blood Parameters	Remarks
Ganciclovir	6 mg/kg twice daily, intravenous, per 6 weeks.	Total Leucocyte Count (TLC), renal and liver function tests, blood electrolytes estimation	Stop treatment if absolute neutrophil count < 500 cells/mm ³ or platelet count < 25 000 cells/mm ³
Valganciclovir	15 mg/kg twice daily, per OS, per 6 weeks.	Total Leucocyte Count (TLC), renal and liver function tests, blood electrolytes estimation	Stop treatment if absolute neutrophil count < 500 cells/mm ³ or platelet count < 25 000 cells/mm ³

Source- Gandhi RS, Fernandez-Alvarez JR, Rabe H. Management of congenital cytomegalovirus infection: an evidence-based approach. *Acta Paediatrica* 2010; 99: 509-515.

Prevention

High-risk cases such as patients undergoing organ transplantation, immune deficient and premature infants are ideal subjects for CMV prophylaxis. Screening of blood and organ donors for CMV virus and its products is a routine clinical practice and use of CMV immunoglobulins are advocated in prevention. Acyclovir is a useful prophylactic drug but not useful in treatment. No effective vaccines are available so far. Live attenuated vaccines such as Towne 125 and AD 169 strains and a purified CMV polypeptide vaccines are under clinical trial and have been found to be immunogenic but not effective in protecting immunocompromised individuals from CMV infection. Horizontal transmission of CMV requires direct contact with infected materials that contain the virus. Adherence to standard precautions with good hand hygiene is effective to prevent CMV infection.⁵⁰ Preexisting maternal immunity to CMV affords significant protection to the fetus. The overall risk for delivering a symptomatic neonate is about 5% with primary maternal CMV infection.⁵¹ Women of childbearing age should have CMV serological tests as routine screening procedure for any congenital infections including TORCH group of organisms. Health care professionals should provide care for young children who are potential CMV excretors and pregnant women who are CMV seronegative with information on prevention measures.⁵² Although newborn hearing screening programs may miss the late-onset hearing loss complicated in congenital CMV infection, routine screening of all newborns for CMV is not yet recommended.⁵³

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