# Case Series of Congenital Cytomegalovirus Infection in Neonatal Period

## Yenidoğanda Konjenital Sitomegalovirus Enfeksiyonu: Vaka Serisi

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**ABSTRACT**

**Objective:** Cytomegalovirus (CMV) is one of the most common cause of congenital infections in the newborn. CMV infection is a multisystem disease, which symptomatic infants generally present with intrauterine growth restriction, hepatosplenomegaly, cholestasis, rash, thrombocytopenia, and microcephaly.
**Methods**: Retrospective chart review was performed for newborns who were diagnosed with congenital CMV infection at tertiary neonatal intensive care unit (NICU) in Turkey, between October 2012 and January 2015.
**Results:** We identified eight cases with congenital CMV infection with an incidence of 0.15 % among admitted neonates. Mean gestational age and birth weight of cases were 32.6 (±4.2) weeks and 1591 (±681) g respectively. Six (75%) cases were premature. The symptoms at presentation were as follows; thrombocytopenia, cholestatic hepatitis, blue-berry muffin rash, intracranial calcification, microcephaly, pneumonia, and bilateral cataract. Five cases were treated with ganciclovir. Three of them died in follow-up.
**Conclusion:** Congenital CMV infection is an important cause of neonatal morbidity and mortality. Physicians should be aware of the preventive measures and postnatal interventions of congenital CMV infection.

**Key Words:** Cytomegalovirus, congenital infection, newborn

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**ÖZET**

**Amaç:** Sitomegalovirus (CMV) yenidoğanda konjenital enfeksiyonların en yaygın nedenidir. CMV enfeksiyonu semptomatik infantlarda genellikle intrauterin büyüme geriliği, hepatosplenomegali, kolestaz, döküntü, trombositopeni ve mikrosefali ile bulgu veren olan multisistemik bir hastalıktır**.**
**Yöntem:** Ekim 2012 ve Ocak 2015 yılları arasında, 3. düzey yenidoğan yoğun bakım ünitesinde konjenital CMV tanısı alan olguların verileri retrospektif olarak değerlendirildi.
**Bulgular:** Çalışma süresince 8 olgu konjenital CMV tanısı aldı. Yoğun bakım ünitesine kabul edilen yenidoğanlar arasında konjenital CMV insidansı % 0, 15 olarak belirlendi. Olguların ortalama doğum haftası ve doğum ağırlığı 32, 6 (±4, 2) hafta ve 1591 (±681) gramdı. Altı (%75) olgu premature idi. Olguların tanı anında bulguları trombositopeni, kolestatik hepatit, blue-berry muffin döküntüsü, intrakraniyal kalsifikasyon, mikrosefali, pnömoni and bilateral kataraktı. Beş olguya gansiklovir ile tedavi başlandı. Üç olgu izlemde exitus oldu.
**Sonuç:** Konjenital CMV enfeksiyonu neonatal morbidite ve mortalitenin önemli bir nedenidir. Doktorlar konjenital CMV enfeksiyonunu önleyici yaklaşımların ve doğum sonrası müdahalelerin farkında olmalıdır.

**Anahtar Sözcükler:** Sitomegalovirus, Konjenital enfeksiyon; Yenidoğan

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## INTRODUCTION

Cytomegalovirus (CMV) is one of the most common causes of congenital infections in the fetus and neonate, with an incidence of 0.2% to 2.4% of live births. However, the incidence of congenital infection among different populations is variable (1). Although most congenital CMV infections are asymptomatic, the virus can cause a wide range of diseases in symptomatic neonates. The usual clinical manifestations of congenital infection are intrauterine growth restriction (IUGR), prematurity, hepatosplenomegaly, jaundice, conjugated hyperbilirubinemia, hepatitis syndrome, thrombocytopenia, blueberry muffin–like rash, microcephaly, seizure, chorioretinitis, and pneumonitis (2, 3). The most common long term sequeale in infancy and childhood are sensorineural hearing deficits and learning disabilities. A progressive sensorineural hearing loss may develop in 13-15% of asymptomatic newborns (4).

The mortality rate of serious CMV infection is approximately 30% in neonatal period. Most deaths occur in the neonatal period and are usually related to multiorgan diseases with severe hepatic dysfunction, bleeding, disseminated intravascular coagulation, and secondary bacterial infection (5, 6).

In the present study, the incidence, clinical spectrum, and outcome of congenital CMV infections were investigated among preterm and full-term infants in neonatal intensive care unit (NICU).

## METHODS

A retrospective chart review of neonates with congenital CMV infection was performed between October 2012 and January 2015, in Etlik Zübeyde Hanım Women's Health Teaching and Research Hospital, NICU. The diagnosis was based on the presence of CMV-IgM antibodies in serum, and detection of CMV-DNA in serum, cerebrospinal fluid (CSF) and/or urine if there existed any clinical finding supported congenital CMV infection.

Demographic characteristics of patients including gender, gestational age (GA), birth weight (BW), maternal or gestational disease, mode of delivery, and APGAR scores were recorded. Clinical signs and symptoms, postnatal age at diagnosis, treatment, and prognosis were reviewed. Laboratory tests including complete blood count (CBC), hepatic function tests, serum bilirubin levels, electrolytes, serological tests for intrauterine infection, serum CMV antibodies, CMV-PCR in serum, CSF and/or urine, and imaging tests were also documented.

CMV-IgG and CMV-IgM antibodies in serum were determined using microenzyme immunoassay system (ELISA). Index values ≥ 0.5 were considered as positive for CMV-IgM antibodies. CMV Quant kit were performed for quantitative detection of CMV-DNA in copies/ml, in blood, urine and cerebrospinal fluid samples (Roche Applied Sciences). Active CMV infection was diagnosed if specific IgM were positive or/and CMV-DNA were detected in samples. Patients were defined as congenital CMV infection if the virus was isolated from infants within the first 3 weeks of life.

## RESULTS

During the study period, 5029neonates admitted to the NICU, of which eight were diagnosed as symptomatic congenital CMV infection. The incidence of symptomatic congenital CMV infection was found to be 0.15 % of NICU admissions. No gender predominance was observed, that four out of eight cases were male. Mean GA and BW were 32.6 (±4.2) weeks and 1591 (±681) g respectively. Six (75%) patients were premature.

The mean postnatal age at the time of diagnosis was 7.6 (± 6.4) days. All infants' diagnosis at admission to the NICU were respiratory distress and IUGR. The symptoms of cases associated with congenital CMV infection at presentation were as follows; thrombocytopenia, cholestatic hepatitis, blue-berry muffin rash, intracranial calcification, microcephaly, pneumonia, and bilateral cataract. CMV-DNA was isolated in serum and urine of all cases, whereas it was isolated from CSF in three cases.

Five cases were treated ganciclovir. Indications for treatment were hepatitis, and findings of central nervous system including microcephaly, cataract, periventricular calcification, and positive CMV DNA in CSF. Three of them died due to sepsis, fulminant hepatic failure, and intracranial hemorrhage associated with thrombocytopenia. Five patients survived of which the two were on ganciclovir treatment. Three cases (Case 1 – 3) did not require treatment regarding the absence of CMV related findings including chorioretinitis, hepatitis, pneumonitis, central nervous system involvement. The mild thrombocytopenia is the only symptom in those cases. Three untreated and two treated cases had normal the brainstem evoked response audiometry (BERA) before discharge. Microcephaly was present in two cases (Case7 and 8). The cases were detailed in Table 1.

Mothers were found to have incomplete antenatal diagnostic evaluations including serum CMV serology and fetal imaging studies due to irregular antenatal follow-up. Five mothers evaluated for CMV infection after delivery and three out of five mother were found to have positive CMV IgM result (Case 2, 4, 8). Serologic testing for CMV could not been studied in three mothers after delivery because of early discharge of mothers.

**Table 1:**Demographic and clinical features of cases with congenital CMV infection

| Case | GA (weeks) | Gender | BW, g | Mode of delivery | Day of serologic test | Clinical findings | Laboratory findings | Gancyclovir treatment * | Outcome (day) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 30 | M | 1680 | C/S | 13 | Hepatosplenomegaly | Thrombocytopenia, Serum CMV DNA (+) BOS CMV DNA (-) | No | Discharged (62$^{th}$day) |
| 2 | 34 | F | 2080 | VD | 2 | Cholestatic hepatitis | Thrombocytopenia, Serum CMV DNA(+) BOS CMV DNA (-) | No | Discharged (17$^{th}$day) |
| 3 | 37 | M | 1290 | C/S | 10 | Hepatosplenomegaly, IUGR | Thrombocytopenia, Serum CMV DNA(+) BOS CMV DNA (-) | No | Discharged (31$^{th}$day) |
| 4 | 30 | F | 950 | C/S | 2 | Cholestatic hepatitis, Microcephaly, Cataract, IUGR | Thrombocytopenia, serum and CSF CMV DNA (+) | Yes (3 – 12) | Died (12$^{th}$day) |
| 5 | 36 | F | 1700 | C/S | 3 | Hepatosplenomegaly, Hepatitis, IUGR | Thrombocytopenia, serum and CSF CMV DNA (+) | Yes (5 – 22) | Died (22$^{th}$day) |
| 6 | 26 | M | 1080 | VD | 18 | Blueberrymuffinrash, Cholestatic hepatitis | Serum and CSF CMV DNA (+) | Yes (25-33) | Died (33$^{th}$day) |
| 7 | 30 | F | 1150 | C/S | 1 | IUGR | Thrombocytopenia, serum CMV DNA(+) Periventricularcalcification | Yes (6 – 48) | Discharged (69$^{th}$day) |
| 8 | 38 | M | 2800 | C/S | 12 | Pneumonia, | Thrombocytopenia, CSF and serum CMV DNA (+)Periventricularcalcification | Yes (17 – 59) | Discharged (29$^{th}$day) |

*Numberswithinparanthesisreferstodays of initiation and termination of gancyclovirtreatment
C/S: cesariansection, VD: vaginaldelivery, IUGR: Intrauterinegrowthretardation, CSF: cerebrospinalfluid

## DISCUSSION

The incidence of congenital CMV infection was reported as 6.8%, 1% and 0.8% in the NICUs with CMV screening program for all admitted infants. However, it was reported that approximately 10 percent of these infants had clinical symptoms (7, 8). Similar to these findings, incidence of symptomatic congenital CMV infection was found to be 0.15 % in our NICU. We couldn't routinely perform CMV screening in all infants.

The clinical presentation of symptomatic congenital CMV infection can range from mild nonspecific findings to multiple organ system involvement. The most commonly observed physical findings are petechiae, jaundice at birth, hepatosplenomegaly, small size for gestational age, prematurity, microcephaly, hypotonia, and poor suck. Chorioretinitis and/or optic atrophy are detected in approximately 10% of symptomatic infants (2, 9). The most common clinical manifestations in our study were IUGR (n=4) and prematurity (n=6). Three patients presented cholestatic hepatitis. Several studies showed the higher prevalence of CMV in infants with neonatal cholestasis (10). The role of CMV infections in the pathogenesis of cholestatic hepatitis is still not clear.

The gold standard for diagnosis of congenital CMV infection in newborns is the isolation of the virus in body fluids within the first 3 weeks of life. Detection of viral DNA by PCR is rapidly replacing viral culture as a rapid, sensitive, and efficient method of diagnosing CMV infection (11). Both false-positive and false-negative test results may occur with CMV IgM assays, and serologic assays are not enough to exclude CMV infection in neonates (12). Presence of CMV-DNA in serum in addition to characteristic clinical findings as cholestasis, hepatosplenomegaly, blue-berry muffin rash, and thrombocytopenia were considered to be diagnostic for CMV infection, and a viral culture was not ordered in cases.

In congenital CMV infection, mortality rates of up to 10% to 30% have been reported. Most deaths occur in the neonatal period and are usually related to multiorgan diseases with severe hepatic dysfunction, bleeding, disseminated intravascular coagulation, and secondary bacterial infections (13). Antiviral therapy for congenital CMV infection appears to be useful in ameliorating the severity of central nervous system disease and focal organ diseases, including hepatitis and pneumonitis (11). Ganciclovir treatment was started in five cases due to hepatitis, and central nervous system disease. Three out of five treated cases died due to sepsis, fulminant hepatic failure and intracranial hemorrhage.

CMV seroprevalence rates in our country in women of childbearing age were reported in the range of 87.8%-100% and 92.6%-97.3% (14, 15). The high rates for CMV serology are closely related to the level of community and poor hygienic conditions. Therefore, positive CMV serology has a confident impact and could significantly reduce the incidence of maternal CMV infection and its unfavorable effects during pregnancy (16). The effective strategy for prevention of congenital CMV infection is behavioral and educational interventions in CMV seronegative women.

Although the absence of regular antenatal follow-up limited us to conclude that if CMV infections were primary, re-infection or recurrence, the cases we presented demonstrated the high incidence of the disturbing morbidities associated with congenital CMV infection and highlighted the significance of antenatal preventive measures and postnatal interventions. Infants have CMV infection require close and intense pediatric follow-up. They should be enrolled in early childhood intervention programs including physical, occupational, and speech therapy.

**Conflict of interest:**
No conflict of interest was declared by the authors.

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