



Evaluation of Patients Treated for the Symptomatic Congenital Cytomegalovirus Infection

Semptomatik Konjenital Sitomegalovirüs Enfeksiyonu Nedeniyle Tedavi Edilen Hastaların Değerlendirilmesi

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Abstract

Objective: Our current knowledge for the management of symptomatic congenital cytomegalovirus (CMV) infections is limited to few studies. In our study, we aimed to present the data of our patients, who were treated for the diagnosis of symptomatic congenital CMV infections.

Material and Methods: A total of 19 patients with the diagnosis of congenital CMV infection treated at our tertiary center hospital between 2015-2021 were retrospectively included in the study. Antiviral treatment (ganciclovir/valganciclovir) was administered to all patients for six months.

Results: Five (26.4%) patients were diagnosed with congenital CMV infection within the first three weeks of life. Treatment indications were hearing loss in 12 (63.2%) patients, central nervous system involvement in 7 (36.8%) patients and cholestasis in 6 (31.6%) patients. Six patients had more than one indication. There was no case with eye involvement. Six (31.6 %) patients had pathological findings in cranial imaging and 8 (42.1%) patients had pathological findings in abdominal imaging. Median blood CMV PCR was 1.538 IU/mL (IQR= 850-9.961) and median urine CMV PCR was 425.585 copies/mL (IQR= 111.370-10.105.585). As the side effect of treatment, neutropenia developed in two patients (10.5%). However, no permanent side effect of the treatment was observed. Mean follow-up period was 16.63 ± 8.1 months. Seven (36.8%) patients had chronic sequela of the disease (hearing loss and central nervous system involvement).

Conclusion: Ganciclovir/valganciclovir treatment is safe for the treatment of congenital CMV infections.

Keywords: Cytomegalovirus infections, ganciclovir, hearing loss, microcephaly, valganciclovir

Öz

Giriş: Semptomatik konjenital sitomegalovirüs (CMV) enfeksiyonlarının yönetimine ilişkin mevcut bilgilerimiz az sayıda çalışmayla sınırlıdır. Çalışmamızda semptomatik konjenital CMV enfeksiyonu tanısı ile tedavi edilen hastalarımızın verilerini sunmayı amaçladık.

Gereç ve Yöntemler: Üçüncü basamak hastanemizde 2015-2021 yılları arasında tedavi edilen konjenital CMV enfeksiyonu tanısı ile toplam 19 hasta retrospektif olarak çalışmaya dahil edildi. Tüm hastalara altı ay süreyle antiviral tedavi (gansiklovir/valgansiklovir) uygulandı.

Bulgular: Beş (%26.4) hastaya yaşamın ilk üç haftasında konjenital CMV enfeksiyonu tanısı kondu. Tedavi endikasyonları 12 (%63.2) hastada işitme kaybı, 7 (%36.8) hastada merkezi sinir sistemi tutulumu ve 6 (%31.6) hastada kolestaz idi. Altı hastada birden çok endikasyon mevcuttu. Göz tutulumu olan olgu yoktu. Altı (%31.6) hastada kranial görüntüleme patolojik bulgular, 8 (%42.1) hastada abdominal görüntüleme patolojik bulgular saptandı. Medyan kan CMV polimeraz zincir reaksiyonu (PCR) 1.538 IU/mL (IQR= 850-9.961) ve medyan idrar CMV PCR'si 425.585 kopya/mL'dir (IQR= 111.370-10.105.585). Tedavinin yan etkisi olarak iki hastada (%10.5) nötropeni gelişti. Ancak tedavinin kalıcı bir yan etkisi gözlenmedi. Ortalama takip süresi 16.3 ± 8.1 aydı. Yedi (%36.8) hastada hastalığın kronik sekeli (işitme kaybı ve merkezi sinir sistemi tutulumu) vardı.

Sonuç: Gansiklovir/valgansiklovir tedavisi konjenital CMV enfeksiyonlarının tedavisinde hem güvenli hem de etkilidir.

Anahtar Kelimeler: Sitomegalovirüs enfeksiyonları, gansiklovir, işitme kaybı, mikrosefali, valgansiklovir

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Introduction

Congenital cytomegalovirus (CMV) infection is the most common congenital infection worldwide and is estimated to have an incidence of 0.6-0.7% in developing countries (1). In developed countries such as the United States, it is reported that approximately 40,000 babies are born with congenital CMV infection each year (2). Babies acquire the disease from their mothers. While the risk of vertical transmission to the fetus is around 30% in primary maternal infection, it is around 1.4% in recurrent infections (3). Approximately 10-15 percent of newborns with congenital CMV infection present with symptoms at birth (4). It is the leading cause of non-hereditary sensorineural hearing loss and it can cause long-term neurodevelopmental sequelae such as cerebral palsy, visual impairment and seizures. Other clinical findings observed at birth include jaundice, hepatosplenomegaly, petechiae, small for gestational age birth, chorioretinitis and microcephaly (5). Newborn infants infected as a result of the mother's primary infection are more likely to be symptomatic at birth and develop long-term sequelae than infants infected by the mother's recurrent CMV infection (6). About 8-10% of neonates born with the diagnosis of congenital CMV infection may develop serious life-threatening diseases such as sepsis and myocarditis, and in general, mortality rate in neonates with the diagnosis of congenital CMV is around 4-8% in the first year of their lives (7,8). Therefore, it is very important to diagnose as early as possible.

Clinical suspicion and laboratory tests play a significant role in the diagnosis. Laboratory identification of congenital CMV infection is possible by isolation or molecular detection of CMV virus from urine or saliva samples taken from the patient during the first three weeks of life (9). There are two important drugs currently used in symptomatic congenital CMV infection; the first of these is ganciclovir for intravenous use, and the second is valganciclovir, which is the oral form. It has been shown that patients treated with these drugs have better long-term audiological and neurodevelopmental outcomes (10,11).

In this study, it was aimed to present the data of our patients who were treated with the diagnosis of symptomatic congenital CMV infection.

Materials and Methods

This retrospective descriptive study was conducted in a tertiary city hospital in İstanbul, Türkiye. The data of 19 patients between May 2015 to December 2021 were retrospectively evaluated. The participants were identified through the department's patient files archive (age, sex, clinical findings, microbiological findings [serologic tests for CMV and polymerase chain reaction (PCR) for urine and plasma samples,

radiological findings and drug adverse events]. All patients underwent pre-treatment hearing test, eye examination, abdominal ultrasonography, and cranial imaging [cranial ultrasonography or computed tomography (CT)]. Cytomegalovirus PCR was studied in blood and urine samples of all patients. In addition, CMV IgM and CMV IgG tests were studied from all participants.

Case (symptomatic congenital CMV) definition was made as follows: Patients with symptomatic clinical findings within three weeks after birth and CMV PCR positivity in blood and/or urine (12). For infants older than three weeks, diagnosis was made with system involvement, serology tests and CMV PCR tests in blood and urine.

In accordance with the protocol of the Ministry of Health of our country, consent was obtained from the families of the patients who were planned to initiate valganciclovir oral therapy for the diagnosis of symptomatic congenital CMV, and then an off-label application was made to the Ministry of Health. After approval was obtained, all participants received valganciclovir (at a dose of 16 mg per kilogram of body weight, orally twice daily) for six months (13). We used intravenous ganciclovir initially for the treatment of congenital CMV infection in infants who had life-threatening disease (viral sepsis-like syndrome, severe and refractory thrombocytopenia, etc.) or gastrointestinal problems like absorption of enteral medications. Intravenous ganciclovir treatment was initiated at 6 mg/kg/dose every 12 hours, and then oral valganciclovir treatment was continued and the total treatment was given for six months (14). Weekly complete blood count examinations were taken from the patients who received treatment for the first six weeks, and if the tests were stable, the intervals were increased to two weeks. Weekly liver and kidney function tests were taken from the patients who received treatment during the early stages of the treatment, and if the tests were stable, the intervals were increased to two to three weeks (9,15). During the six-month period in which the study data were evaluated, the patients were evaluated in terms of eye findings and hearing functions at three-month intervals. All patients were referred to a child development specialist in terms of their neuromotor development evaluation.

Statistical Analysis

Normally distributed quantitative variables were expressed as mean \pm standard deviation, whereas non-normally distributed quantitative variables were expressed as median with interquartile ranges (IQR). All analyses were conducted using SPSS 25 software (IBM SPSS Statistics, New York).

This study was approved by the medical research ethics committee of our institution. (Report no: 2021/514/214/10)

Results

A total of 19 patients were included in the study. Six of the cases (31.6%) were females and 13 (68.4%) were males. Among all cases, 26.3% of the cases were diagnosed within the first three weeks of life. Median age of the patients diagnosed with congenital CMV infection was 60 days (IQR= 21-120). Mean birthweight of the patients was 2440 ± 829 gr. Seven (36.8%) patients had history of preterm birth and 4 (21.1%) patients were small for gestational age at birth. Indications for treatment were hearing loss (63.2%), central nervous system involvement (36.8%) and cholestasis (31.6 %). Six patients had more than one indication. Four patients had both hearing loss and cholestasis, and two patients had hearing loss and CNS involvement. There was no case with eye involvement. Eight (42%) patients had abnormal findings in abdominal imaging and six (31.6%) patients had abnormal findings in cranial imaging (tomography). Demographic characteristics and the clinical findings of the patients are summarized in Table 1.

Table 1. Demographic and clinical characteristics of the infants with congenital CMV infection

Age (days)	
median (IQR)	60 (21-120)
Sex n (%)	
Female	6 (31.6)
Male	13 (68.4)
Birth weight (gr)	
mean ± SD	2440 ± 829.4
Preterm birth n (%)	7 (36.8)
Small size for gestational age n (%)	4 (21.1)
Age at diagnosis n (%)	
1 week	4 (21.1)
1-3 weeks	1 (5.3)
3 weeks-3 months	10 (52.6)
>3 months	4 (21.1)
Symptoms n (%)	
Neurologic manifestations	7 (36.8)
Cholestasis	6 (31.6)
Splenomegaly	5 (26.3)
Hepatomegaly	4 (21.1)
Thrombocytopenia	3 (15.8)
Microcephaly	3 (15.8)
Petechiae	2 (10.5)
Hearing loss n(%)	
Unilateral	8 (42.1)
Bilateral	4 (21.1)

Table 2. Laboratory values of the patients

Blood CMV PCR (IU/mL)	
median (IQR)	1.538 (850-9.961)
Urine CMV PCR (copy/mL)	
median (IQR)	425.585 (111.370-10.105.585)
Serology n (%)	
CMV IgG seropositivity	18 (94.7)
CMV IgM seropositivity	12 (63.2)
Hemoglobin (g/dL)	
mean ± SD	11.12 ± 3.78
Leukocyte count (10³/μL)	
mean ± SD	12.6 ± 4.96
Absolute neutrophil count (10³/μL)	
median (IQR)	2.6 (2-5.3)
Platelet count (10³/μL)	
mean ± SD	365.11 ± 191.41
ALT (U/L)	
median (IQR)	37 (20-94)
AST (U/L)	
median (IQR)	59 (43-113)
GGT (U/L)	
median (IQR)	55 (41-107)
PCR: Polymerase chain reaction, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase GGT: Gamma glutamyl transferase, IQR: Interquartile range.	

Median blood CMV PCR was 1.538 IU/mL (850-9.961), and median urine CMV PCR was 425.585 copies/mL (111.370-10.105.585). One patient was found to have positive CMV PCR result in the cerebrospinal fluid. Laboratory results of patients are shown in Table 2.

Twelve (63.2%) patients were initially treated with IV ganciclovir. Mean ganciclovir treatment duration was 20.3 ± 6.5 days. According to the treatment protocol, oral valganciclovir was given alone to seven patients for six months duration.

During the treatment period, patients were followed closely in terms of drug side effects. Neutropenia developed in two patients (10.5%). However, no permanent side effect of the treatment was observed in the patients.

Mean follow-up period of the patients was 16.63 ± 81 months. Seven (36.8%) patients had sequela of the disease. Of these, three (15.7%) had hearing loss, three (15.7%) had CNS involvement like convulsion, cerebral palsy and microcephaly and one (5.2%) patient had both.

Discussion

Congenital CMV is a challenging disease for clinicians due to its high rates of underdiagnosis, debatable treatment indi-

cations and uncertain efficacy of treatment. Most of the currently available data about the treatment of congenital CMV infection mainly stand on case reports (16-18). To date, the most comprehensive study about the treatment of symptomatic congenital CMV infections in the literature has been conducted by Kimberlin et al., in which they compared the treatment duration of valganciclovir for six months with six weeks in 86 cases. They have concluded that although valganciclovir treatment for six months is not superior to six weeks treatment in the short-term period, it has been shown to have moderately better hearing and developmental results in the long term (11). Based on this study, we decided to give our patients six months of treatment in order to achieve better auditory and developmental results.

Congenital CMV is one of the main causes of non-genetic sensorineural hearing loss at birth, accounting for approximately 25% of all causes, and is responsible for 25% of late-onset sensorineural hearing loss that occurs by the age four (19,20). Other major clinical findings of congenital CMV include hepatosplenomegaly, small size for gestational age, microcephaly, petechiae, jaundice at birth, chorioretinitis, and pneumonia (21). In a meta-analysis published by Zhang et al. with a total of 4.262 participants with 1.114 neonates in the CMV group and 3.148 neonates in the control group, it has been shown that hearing loss and microcephaly are significantly higher in the infected group (22). In another study by Dahle et al., having a symptomatic disease has also been emphasized to be an important risk factor for hearing loss (23). They have reported sensorineural hearing loss at a rate of 7.4% in asymptomatic cases whereas they have found it to be 40.7% in the symptomatic group (23). Interestingly, in the study of Pathirana et al., 34 patients with congenital CMV have been compared with 74 control patients, and it has been stated that there is no significant difference in terms of neurological sequelae between the groups at the end of 12 months. However, they have also suggested that long-term results should also be evaluated (24). In our study, hearing loss was found to be the most common clinical finding in congenital CMV cases and CNS involvement was the second. During the mean 16 months of follow-up of our patients, 4% of the patients had CNS involvement and 4% had persisting hearing loss.

Neutropenia, thrombocytopenia, mild elevation of transaminase levels and nephrotoxicity may be expected with ganciclovir and valganciclovir treatment (25,26). Neutropenia is the most common side effect of ganciclovir. Two retrospective studies have found that 46-52% of the babies treated have developed neutropenia (27,28). In a meta-analysis by Wang et al., 8.8% of 340 newborns treated for CMV infection with intravenous ganciclovir have developed life-threatening neutropenia (absolute neutrophil count < 0.5 x 10⁹/L).

The rates of neutropenia and thrombocytopenia have been reported to be 25.6% and 6.2%, respectively. All cases of neutropenia have been reported to be resolved either after cessation of treatment or dose reduction (25). Among our cases, 10.5% also developed neutropenia during treatment. However, one week after the cessation of treatment, it spontaneously resolved and neutropenia did not recur after reinitiation of the treatment.

Major limitations of our study are its relatively low sample size and relatively short follow-up period. Furthermore, we did not have a control group with congenital CMV infection to whom we did not give treatment.

Consequently, long-term treatment of congenital CMV infection with IV ganciclovir and oral valganciclovir seems to be safe. Therefore, the treatment of congenital CMV cases should not be withheld due to the fear of side-effects of treatment. However, since there was no control group in our study and our patients did not have longer follow-up results, it would not be correct to speak clearly about effectiveness. Therefore, in order to better demonstrate the effect of antiviral therapy on long term sequelae, more studies with longer follow-ups are still needed.

Ethics Committee Approval: This study was approved by Kartal Dr. Lütfi Kırdar City Hospital Clinical Research Ethics Committee (Decision no: 2021/514/214/10, Date: 30.11.2021).

Informed Consent: Patient consent was obtained.

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