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ORIGINAL RESEARCH
Neonatology

Evaluation of cases followed up due to congenital and perinatal cytomegalovirus infection

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ABSTRACT

Objective: Cytomegalovirus (CMV), the most common congenital infection agent, is transmitted transplacentally to the baby during pregnancy. It is defined as congenital CMV (cCMV) when detected in body fluids within the first three weeks of life. This study aimed to retrospectively investigate the clinical, laboratory, and treatment outcomes of patients diagnosed with cCMV.

Material and Methods: Between January 2015 and June 2023, the medical records of patients diagnosed with congenital/perinatal CMV (CMV identified in plasma and/or urine PCR) from the Neonatal Intensive Care Unit and neonatal outpatient clinic were retrospectively evaluated. Patients diagnosed within the first 21 days of life were categorized as Group 1 cCMV, while those diagnosed after 21 days were considered Group 2 congenital/perinatal CMV.

Results: A total of 23 patients were included in the study, with 5 in Group 1 and 18 in Group 2. In Group 1, the mean age at diagnosis was 13 days (range: 6–19 days), gestational age was 37.6±0.9 weeks, and birth weight was 2611±121 grams. In Group 2, the patients had a mean age of 49 days (range: 23–151 days), gestational age of 30.1±4.4 weeks, and birth weight of 1333±618 grams. All patients in Group 1 were male, while 50% (9 cases) of Group 2 were male. Ganciclovir treatment was initiated for five patients in Group 1 and 14 patients in Group 2. Neutropenia, thrombocytopenia, and abnormal liver function tests were observed in Group 1 in 1 (20%), 3 (60%), and 1 (20%) of cases, respectively; in Group 2, they were observed in 9 (50%), 6 (33.3%), and 3 (16.7%) of cases, respectively. Intracranial calcification and microcephaly were observed in 2 cases (40%) and 1 case (20%) in Group 1, respectively; in Group 2, they were observed in 1 case (5.6%) and 3 cases (16.7%), respectively.

Conclusion: Despite being the most common congenital infection, diagnosing congenital CMV in the neonatal period is often challenging due to non-specific and non-pathognomonic symptoms. Plasma/urine CMV PCR examination, cranial imaging, and hearing assessment are crucial for diagnosing suspected cCMV cases. This study evaluates the clinical, laboratory, and treatment findings of patients diagnosed with cCMV.

Keywords: Congenital CMV infection; early diagnosis; newborn; sensorineural hearing loss.

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Konjenital ve perinatal sitomegalovirüs enfeksiyonu nedeniyle takip edilen olguların değerlendirilmesi

ÖZET

Amaç: Dünyada en sık konjenital enfeksiyon etkeni olan sitomegalovirüsün (CMV), sıklıkla gebelik sırasında bebeğe transplasental yolla bulaşı sonucunda, hayatın ilk üç haftasında vücut sıvılarında saptanması konjenital CMV (cCMV) olarak tanımlanmaktadır. Bu çalışmada, cCMV tanısı konulan hastaların klinik, laboratuvar ve tedavi sonuçlarının retrospektif olarak incelenmesi amaçlanmıştır.

Gereç ve Yöntemler: Ocak 2015–Haziran 2023 tarihleri arasında yenidoğan yoğun bakım ünitesinde ve yenidoğan polikliniğinde izlenen, konjenital/perinatal CMV tanılı (plazma ve/veya idrar PCR'da CMV saptanan) hastaların dosya kayıtları incelenmiştir. Demografik özellikler, klinik bulgular, laboratuvar sonuçları ve tedaviler retrospektif olarak değerlendirildi. Yaşamın ilk 21 gününde tanı alan hastalar Grup 1 cCMV, 21 günden sonra tanı alanlar Grup 2 konjenital/perinatal CMV olarak değerlendirildi.

Bulgular: Grup 1'de 5, Grup 2'de 18 hasta olmak üzere toplam 23 hasta çalışmaya alındı. Grup 1'deki hastaların tanı yaşı ortalama 13 (6–19) gün, gestasyon yaşları 37.6±0.9 hafta, doğum ağırlıkları 2611±121 gram idi. Grup 2'deki hastaların yaşları ortalama 49 (23–151) gün, gestasyon yaşları 30.1±4.4 hafta, doğum ağırlığı 1333±618 gram idi. Grup 1'deki hastaların cinsiyeti tümü erkek iken, Grup 2'dekilerin %50'si (9 olgu) erkekti. Grup 1'deki beş hastaya, Grup 2'deki 14 hastaya gansiklovir tedavisi başlandı. Nötropeni, trombositopeni ve anormal karaciğer fonksiyon testleri Grup 1'de sırasıyla 1 (%20), 3 (%60), 1 (%20); Grup 2'de 9 (%50), 6 (%33.3), 3 (%16.7) olarak saptandı. İntrakranial kalsifikasyon ve mikrosefali sırasıyla Grup 1'de 2 (%40), 1 (%20); Grup 2'de 1 (%5.6), 3 (%16.7) olarak değerlendirildi.

Tartışma: Konjenital CMV enfeksiyonu, en sık görülen konjenital enfeksiyon olmasına rağmen bulguları hastalığa özel ve patognomonik olmadığı için tanısının yenidoğan döneminde konulması çoğu zaman mümkün olamamaktadır. Konjenital CMV enfeksiyonu düşünülen hastalarda plazma/idrar CMV PCR incelemesi, kraniyal görüntüleme ve işitmenin değerlendirilmesi tanı için önemlidir. Bu çalışmada, cCMV tanısı konulan hastaların klinik, laboratuvar ve tedavi bulguları değerlendirilmiştir.

Anahtar Kelimeler: Erken tanı; konjenital CMV enfeksiyonu; sensörinöral işitme kaybı; yenidoğan.

INTRODUCTION

The seroprevalence of CMV infection, widely observed worldwide, varies according to geographical, socioeconomic conditions, and age. CMV, referred to as Human Herpesvirus-5, is an enveloped DNA virus, part of the Herpesviridae family, characterized by a double-stranded structure and approximately 200 nm in size. In congenital CMV infection, the detection of viral DNA in blood, saliva, and urine via polymerase chain reaction (PCR) during the first three weeks of life is preferred due to its high sensitivity and specificity (1, 2).

Although the majority of CMV infections during pregnancy are asymptomatic, severe illness can manifest in fetuses and newborns. Primary infection with CMV in seronegative expectant mothers during pregnancy leads to vertical transmission at a rate of 30%, while reactivation or reinfection in seropositive cases results in a transmission rate of 3% (2–4). Vertical transmission from mother to infant primarily occurs through transplacental means during pregnancy, although reports of transmission during birth or via breastfeeding exist at lower rates. Congenital CMV infection, affecting approximately 0.7% of live births worldwide, manifests asymptomatically in around 85-90% of affected infants, predominantly via transplacental transmission, and is associated with neurological sequelae. Besides sensorineural hearing loss, the most common sequela, other complications such as microcephaly, chorioretinitis, cerebral palsy, and cognitive impairments are observed (1, 5–7).

The first among the two important drugs used in the treatment of symptomatic cCMV infection is ganciclovir, administered intravenously, while the second is its oral form, valganciclovir. Studies indicate that patients treated with these medications exhibit better long-term audiological and neurodevelopmental outcomes (8, 9). Dorfman et al. (7) have shown positive outcomes in infants starting valganciclovir treatment after the fourth postnatal week. Cases with sensorineural hearing loss due to cCMV, receiving antiviral treatment, also exhibit improved responses to rehabilitation following cochlear implantation (1). Approximately 10% of asymptomatic cCMV-infected newborns at birth may develop subsequent hearing loss; therefore, it is essential to monitor cases diagnosed with cCMV for hearing impairment (1).

This retrospective study aims to evaluate cases monitored due to congenital and perinatal CMV infection in our neonatal intensive care unit (NICU) and underscore the significance of screening during the perinatal period.

MATERIAL AND METHODS

All patients admitted to our NICU between January 2015 and June 2023, who were screened for possible cCMV infection for various reasons, underwent a search in the hospital's records system. Serum CMV-IgM and IgG levels were routinely assessed in cases where CMV IgM positivity was detected during pregnancy follow-up, as well as in accordance with service protocols for cases potentially indicative of cCMV infection based on gestational age (GA) <10th percentile, small

for gestational age (SGA), intrauterine growth restriction (IUGR), microcephaly, neonatal encephalopathy, abnormal liver function, cholestasis, anemia, thrombocytopenia, neutropenia, and intracranial calcifications observed in cranial imaging.

In our institution, the micro-particle immunoassay method is employed for the determination of serum CMV IgG and IgM antibodies. Positive antibody levels are considered as ≥1 U/ml for CMV-IgG and ≥1 index for CMV-IgM. Patients with detected positive CMV IgG and/or CMV IgM levels underwent assessment of CMV viral load through PCR analysis of viral DNA in serum and/or urine.

The demographic characteristics (gestational age, birth weight, head circumference, gender, age at diagnosis), clinical and laboratory findings (neutropenia, thrombocytopenia, abnormal liver function tests, serum CMV IgG-IgM, serum and/or urine CMV-PCR), cranial imaging, hearing test results, the presence of chorioretinitis, and treatment modality were recorded for patients with positive serum and/or urine CMV PCR values. To assess the antenatal period, maternal CMV serologies were retrospectively investigated from patient records.

Patients presenting with symptoms within the first three weeks postpartum (IUGR, thrombocytopenia, intracranial calcification, cholestasis, encephalopathy, hearing loss) and testing positive for CMV PCR in blood and/or urine were categorized as Group 1 and classified as symptomatic cCMV infection (10). Patients exhibiting organ involvement (SGA, IUGR, thrombocytopenia, abnormal liver function, neutropenia, microcephaly, intracranial calcification) after the initial three postnatal weeks, with confirmed CMV through serological tests and blood and/or urine PCR, were included in Group 2.

Cases receiving erythrocyte transfusions prior to the detection of CMV infection were identified. In our institution, the routine use of leukocyte filters and irradiated blood products is implemented for transfusions to infants to mitigate CMV infection transmission from transfused blood products.

In our unit, treatment involves initiating intravenous (IV) ganciclovir therapy at a dose of 6 mg/kg/dose every 12 hours. Following obtaining consent from the families of patients planned for symptomatic cCMV infection diagnosis using oral valganciclovir per the Ministry of Health protocol, an application is made to the Ministry of Health. Patients undergoing treatment receive weekly blood counts, liver and kidney function tests in the early stages, with test intervals extended to 2–3 weeks if results remain stable (4, 10). After 2–6 weeks of IV treatment, patients are discharged on oral valganciclovir (16 mg/kg, twice daily, orally), and the total treatment duration is completed within six months through outpatient follow-ups (11). Patients under follow-up in the high-risk infant surveillance clinic are also monitored by the Departments of Infectious Diseases, Ophthalmology, Audiology, and Developmental Pediatrics.

This study was conducted with the approval of our hospital's Clinical Research and Ethics Committee (Date: 04.07.2023, Decision No: B.10.1.TKH.4.34.H.GP.0.01/256). The study complied with the principles of the Declaration of Helsinki.

Statistical Analysis

The statistical analysis of the collected patient data was carried out using IBM Statistical Package for the Social Sciences (SPSS) version 23.0 for Windows (IBM Corp., Armonk, NY). Frequency and percentage were utilized to describe categorical data, while mean, standard deviation, median, lower limit, and upper limit were used as descriptive statistics for continuous data. The Mann-Whitney U test was applied for comparing the means of continuous variables between two groups. A statistical significance level of $p<0.05$ was considered in the study.

RESULTS

During the 8-year study period, hospital information system records indicated that out of 10,419 neonates admitted to the 60-bed NICU and 62,324 newborns attending our outpatient clinic, 1,679 were screened for possible cCMV infection based on CMV IgG-IgM tests. Among these, those with positive IgM or high IgG titers (>250 U/ml) underwent further plasma and/or urine CMV PCR analysis. Of the identified cases with positive plasma and/or urine CMV PCR (totaling 28 patients), data from 23 patients were accessible and included in the study.

Based on the examination and diagnostic timing, 5 cases diagnosed within the first 21 days were categorized as Group 1 for cCMV, while 18 cases diagnosed after 21 days were considered Group 2 for congenital/perinatal CMV.

CMV-IgM positivity was detected in only three cases in Group 1, with all patients undergoing plasma and urine CMV-PCR analysis, revealing median (lower-upper) values of 5161 (100–326768) IU/ml and 13,000,000 (1440–156,000,000) copies/ml, respectively. In Group 2, CMV-IgM positivity was identified in 12 patients. Median (lower-upper) plasma CMV-PCR values in 16 patients were 5959 (93–10,183,037) IU/ml, while median (lower-upper) urine CMV-PCR values in 17 patients were 776,247 (1030–16,260,570) copies/ml (Table 1).

When evaluating demographic data, Group 1 had a gestational age (GA), birth weight (BW), and head circumference of 37.6±0.9 weeks, 2611±121 grams, and 33.3±0.8 centimeters, respectively. In contrast, Group 2 had 30.1±4.4 weeks, 1333±618 grams, and 28.1±4.0 centimeters, respectively ($p=0.004$, $p=0.001$, and $p=0.011$). All patients in Group 1 were male, whereas 50% (9 cases) of Group 2 were male. The age at diagnosis for patients was 13 (6–19) days in Group 1 and 49 (23–151) days in Group 2 (Table 2).

When evaluating laboratory findings, neutropenia, thrombocytopenia, and abnormal liver function tests were observed in cases as follows: in Group 1, 1 (20%), 3 (60%), 1 (20%), respectively; in Group 2, 9 (50%), 6 (33.3%), 3 (16.7%), respectively. Central nervous system involvement assessment revealed intracranial calcification and microcephaly as follows: in Group 1, 2 (40%), 1 (20%); in Group 2, 1 (5.6%), 3 (16.7%), respectively (Table 2).

Upon assessing maternal CMV serologies, in Group 1, all four mothers tested positive for IgG antibodies during pregnancy,

Table 1. Demographic and clinical characteristics of cases followed with CMV infection

	Grup 1-congenital CMV (n=5)	Grup 2-congenital/perinatal CMV (n=18)	p
Diagnosis age, (days) median (lower limit-upper limit)	13 (6–19)	49 (23–151)	
Gestational age (weeks), mean±SD	37.6±0.9	30.1±4.4	0.004
Birth weight (g), mean±SD	2611±121	1333±618	0.001
Head circumference (cm), mean±SD	33.3±0.8	28.1±4.0	0.011
Gender, n (%)			
Female		9 (50)	
Male	5 (100)	9 (50)	
Symptom, n (%)			
IUGR	1 (20)	1 (5.6)	
SGA	2 (40)	5 (27.8)	
Encephalopathy	1 (20)	0 (0)	
Intracranial calcification	2 (40)	1 (5.6)	
Microcephaly	1 (20)	3 (16.7)	
Thrombocytopenia	3 (60)	6 (33.3)	
Neutropenia	1 (20)	9 (50)	
Abnormal LFT	1 (20)	3 (16.7)	
Pre-diagnosis BT history, n (%)	0 (0)	8 (44.4)	
Chorioretinitis,n(%)	0 (0)	0 (0)	
Antiviral therapy, n(%)	5 (100)	14 (77.8)	

CMV: Cytomegalovirus; SD: Standard deviation; IUGR: Intrauterine growth retardation; SGA: Small for gestational age; LFT: Liver funcion tests; BT: Blood transfusion.

Table 2. Laboratory results of cases

	Group 1-congenital CMV (n=5)	Group 2-congenital/perinatal CMV (n=18)
Blood CMV PCR (IU/ml), median (lower-upper limit)	5161 (100–326768)	5959 (93–10183037)
Urinary CMV PCR (copies/mL), median (lower-upper limit)	13000000 (1440–156000000)	776247 (1030–16260570)
Serology, n (%)		
CMV IgG seropositive	5 (100)	18 (100)
CMV IgM seropositive	3 (60)	12 (66.7)

CMV: Cytomegalovirus; PCR: Polymerase chain reaction.

while their IgM tests returned negative. In Group 2, among the 13 mothers evaluated, all had positive IgG results, with only one mother exhibiting a positive IgM test. Notably, the pregnant woman who tested positive for IgM displayed low avidity, and CMV was also detected in the baby's PCR. As the diagnosis occurred after 21 days and erythrocyte transfusion had been administered prior to diagnosis, this patient was categorized in Group 2. This particular case, under neonatal unit care due to prematurity, underwent antiviral treatment and exhibited no symptoms except for liver dysfunction.

The cases in Group 1, upon investigation due to reasons including IUGR, SGA, thrombocytopenia, microcephaly, intracranial calcification, cholestasis, encephalopathy, and hearing loss, were diagnosed with cCMV infection upon detection of CMV in postnatal urine PCR on the 13th day (ranging from 6 to 20 days) and plasma PCR on the 13th day (ranging from 6 to 19 days) after birth. As they were symptomatic, ganciclovir treatment was initiated for cCMV infection, followed by a transition to valganciclovir treatment after approval from the Ministry of Health. The treatment duration with oral valganciclovir was completed within six months.

Among the 18 patients in Group 2, who were evaluated at a median of 49 days (ranging from 23 to 151 days) due to neutropenia (9 cases), thrombocytopenia (6 cases), abnormal liver function (3 cases), SGA (5 cases), microcephaly (3 cases), IUGR (1 case), and intracranial calcification (1 case), 14 symptomatic cases did not allow for a clear distinction between congenital and perinatal infection. Therefore, ganciclovir treatment was initiated. Among these 14 cases, eight had received erythrocyte transfusions before CMV investigation. After obtaining approval from the Ministry of Health, treatment was shifted to valganciclovir, and the therapy was completed within six months.

DISCUSSION

In this study, newborns evaluated with a preliminary diagnosis of possible cCMV infection were retrospectively assessed. Among a total of 23 cases where CMV was detected in urine/plasma PCR, 19 (82.6%) were treated, presuming congenital CMV infection. The group of 5 patients identified within the initial 21 days, confirmed with cCMV, and another 14 patients categorized into Group 2, where the differentiation between congenital and perinatal infection couldn't be made due to delayed CMV diagnosis, exhibited higher values in terms of GA and BW.

Congenital CMV infection presents significant challenges for clinicians due to the necessity of diagnosing it within the postnatal 21-day period, controversial treatment indications, and the uncertainty regarding treatment efficacy. The majority of available data for treatment primarily rely on case presentations (10, 12, 13). The detection of the virus in urine PCR is crucial for diagnosis, with urine CMV PCR test exhibiting a sensitivity of 100% and specificity of 99%. A single negative CMV result in a newborn's urine sample is sufficient to exclude the infection (14). Establishing a definitive threshold value for treatment based on the viral load detected via PCR remains unclear due to variations in methods used, hindering the determination of a standardized threshold value. Therefore, it is recommended that each center determines its own threshold value due to these methodological differences (14). In our study, treatment decisions for patients suspected of having cCMV infection were based on values established by our hospital laboratory, considering serial measurements of viral load alongside any increase and organ involvement.

IUGR, SGA, neutropenia, thrombocytopenia, hepatosplenomegaly, cholestasis, jaundice, microcephaly, intracranial calcification, sensorineural hearing loss, and chorioretinitis constitute the main clinical manifestations of congenital CMV infection (10, 15). Assessing our patients in both groups for organ involvement, it was observed that patients in Group 1 predominantly exhibited signs like IUGR and microcephaly, leading to early postnatal investigations, whereas patients in Group 2, often premature infants, were evaluated later due to potential bone marrow involvement of cCMV, particularly presenting with late-onset symptoms like neutropenia and thrombocytopenia.

The most commonly identified neurological outcomes of congenital CMV infection include microcephaly, ventriculomegaly, cerebral atrophy, sensorineural hearing loss, chorioretinitis, and periventricular intracerebral calcifications (15, 16). In symptomatic cases, long-term neurological sequelae such as hearing loss, chorioretinitis, optic atrophy, seizures, mental retardation, delayed motor development and speech, as well as learning disabilities, are observed in approximately 90% of cases (16). In our study, among the pathological findings detected via transfontanelle ultrasound, the incidence of intracranial calcification was 40% in Group 1 and 5.6% in Group 2, with no cases showing any signs of retinitis.

To reduce transfusion-related CMV infection, available options include applying leukocyte filtration or transfusing CMV-negative blood. Third-generation leukocyte filters reduce the level of leukocytes in red cell suspensions from $1x10^8$ to as low as $5x10^6$ or even lower in neonates, significantly decreasing the risk of transfusion-transmitted CMV infection. However, it doesn't completely eliminate the risk. Using CMV-negative blood for transfusions is debatable due to the high prevalence of CMV seropositivity in about 80% of the population and the possibility of serology yielding false-negative results despite infection (17, 18). Guidelines suggest that in the neonatal population, using products with reduced leukocytes is safe instead of CMV-negative blood products (17). Accordingly, in the neonatal intensive care unit (NICU), routinely, blood products with reduced leukocyte content and irradiated components are employed in line with these recommendations. In our study, among the five cases identified as congenital CMV (cCMV) infection, diagnosis was established within the first 21 days, and none had a history of transfusion. For the 14 symptomatic cases diagnosed after 21 days, where the differentiation between congenital and perinatal infection was unclear, antiviral therapy was initiated despite an absence of clear CMV diagnosis prior to erythrocyte transfusion in eight cases. Hence, although the diagnosis of cCMV was not definitively established, treatment was initiated for these individuals.

The use of CMV-seronegative and leukoreduced blood products effectively prevents CMV transmission to very low birth weight (VLBW) infants. However, in this high-risk group, breast milk has been identified as the primary source of postnatal CMV infection (18). A meta-analysis evaluating nineteen studies indicated a higher incidence of CMV infections acquired from breast milk in preterm infants, especially in those fed fresh expressed breast milk. Therefore, the recommendation leans towards using thawed frozen breast milk rather than fresh expressed breast milk for feeding preterm or VLBW infants (19). In extremely preterm infants, long-term adverse outcomes and symptomatic infections have been reported due to CMV acquired through breast milk. This highlights the need for further studies to refine recommendations for cCMV infections (19, 20). In our study, infants diagnosed within the first 21 days (Group 1) weighed over 1500 grams. Among the 18 cases evaluated after postnatal day 21 (Group 2), 11 were born weighing less than 1500 grams. The lack of routine screening for CMV in breast milk or standard practice of

using frozen breast milk contributed as a limitation, hindering the differentiation of congenital and perinatal infections in our study.

Although the long-term effects of congenital CMV infection are known, there's a lack of robust scientific evidence and guidelines in clinical practice for prenatal screening, diagnostic testing in fetuses and newborns, and treatment decisions. Routine screening for CMV in pregnant women is not recommended (14). In our study, when evaluating maternal CMV serologies, in Group 1, all IgGs tested during pregnancy were positive, and all IgMs were negative. In Group 2, which included 18 cases, all mothers had positive IgG levels, while only one mother tested positive for IgM in the serological assessment. Among these cases in Group 2, one mother had a history of maternal CMV infection. This particular case, monitored in the neonatal unit due to prematurity, received antiviral treatment and showed no manifestation except for liver dysfunction.

In a comprehensive study by Kimberlin et al. (21) on the treatment of symptomatic congenital CMV infections, they compared six-week and six-month treatment durations in 86 cases. Although there was no significant difference in the short term, they found better long-term hearing and developmental outcomes with the longer treatment duration. While not eliminating the long-term risk of complications entirely, oral ganciclovir treatment for 6 weeks to 6 months in moderate to severe congenital CMV infections is recommended as an effective and well-tolerated antiviral therapy that may improve hearing and neurodevelopmental outcomes in symptomatic infants (15, 22). In our study, patients initially received parenteral ganciclovir for CMV infection treatment, followed by a transition to oral valganciclovir after obtaining approval from the Ministry of Health and ensuring medication availability. We implemented a six-month treatment plan aiming for better auditory and developmental outcomes in the long term.

Due to the significant impact of sensorineural hearing loss in congenital CMV infection, hearing screening is implemented for all newborns worldwide, including in our country (14). Evidence shows that sensorineural hearing loss can develop in later ages during follow-ups in asymptomatic infants with normal hearing at birth. Given the potential for a delayed, progressive, and fluctuating course of hearing loss, an extensive audiological follow-up is crucial for early diagnosis and treatment in children diagnosed with cCMV. Among our cases, four out of five infants who did not pass the hearing test received antiviral treatment. Upon discharge from our unit, recommendations in the discharge summary emphasize the need for a repeated hearing test for cases followed up due to CMV infection.

Each year, thousands of children face deafness, vision loss, motor, and cognitive impairments due to congenital CMV infection. Recent scientific advancements, such as demonstrating the effectiveness and cost-effectiveness of antiviral treatment in symptomatic infants, have made targeted and universal approaches to CMV screening in newborns achievable. Implementing strategies to prevent congenital CMV and conducting randomized controlled trials are necessary to fill gaps in evaluating antiviral treatment in asymptomatic infants and formulating algorithms. Developing distinct protocols can be beneficial, especially in avoiding diagnostic confusion among very low birth weight infants who have prolonged NICU stays and are likely to undergo at least one red blood cell transfusion.

Among the limitations of our study are the absence of CMV results in all mothers, the lack of investigation for CMV in breast milk, the fact that not all patients were screened for CMV before transfusion, and the inability to access the complete long-term developmental records of the cases.

Ethics Committee Approval: The Ümraniye Training and Research Hospital Clinical Research Ethics Committee granted approval for this study (date: 04.07.2023, number: B.10.1.TKH.4.34.H.GP.0.01/256).

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