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Outcomes in symptomatic preterm infants with postnatal cytomegalovirus infection

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ABSTRACT

Premature infants are at risk for developing symptomatic postnatal cytomegalovirus (CMV) disease, including sepsis-like syndrome. We performed a retrospective case–control study including infants born before 32 weeks of gestation and diagnosed with symptomatic postnatal CMV infection during the neonatal period. Neurodevelopmental outcome was evaluated using the Kyoto Scale of Psychological Development 2001 at 18 months of corrected age and at 3 years of age. Twenty-four infants were diagnosed with postnatal CMV infection; of them, 14 had sepsis-like symptoms and 10 had laboratory test abnormalities only. Home oxygen therapy was used significantly higher in the CMV-positive group compared with the control group at hospital discharge (52% vs 21%, *P*=0.032). The incidence of neurodevelopmental impairment was not significantly different between the two groups at 18 months of corrected age (29% vs 17%, *P*=0.48) and at 3 years of age (43% vs 29%, *P*=0.34). Postnatal CMV infection did not have a significant influence on neurodevelopmental outcomes of symptomatic preterm infants, although those in the CMV-positive group appeared worse. Larger studies with long-term follow-up are needed for a better understanding of continued neurodevelopmental outcomes in preterm infants with postnatal CMV infection.

Keywords: cytomegalovirus infections, premature birth, patient outcome assessment, growth & development, case-control studies

Abbreviations:
BPD: bronchopulmonary dysplasia
CMV: cytomegalovirus
CMV-SLS: cytomegalovirus-related sepsis-like syndrome
DQ: developmental quotient
GCV: ganciclovir
KSPD: Kyoto Scale of Psychological Development
NDI: neurodevelopmental impairment
VLBW: very low birth weight

INTRODUCTION

Very low birth weight (VLBW) infants are at risk for developing symptomatic postnatal cytomegalovirus (CMV) disease, characterized by hepatopathy, thrombocytopenia, neutropenia, petechiae, respiratory distress syndrome, and sepsis-like syndrome, whereas in full-term infants the neonatal clinical course of postnatally acquired CMV infection is usually asymptomatic or very mild.[1,2] A systemic review of VLBW and premature infants, who were born to CMV-seropositive women, reported that the estimated proportions of infants with breast milk-acquired CMV infection, CMV-related symptoms, and CMV-related sepsis-like syndrome (CMV-SLS) were 19%, 10%, and 4%, respectively, among infants who were fed untreated breastmilk.[3]

CMV in breast milk is the main source of CMV infection during the first year of life.[4,5] Nonetheless, breastfeeding is recommended since the benefits of feeding human milk from seropositive mothers to preterm infants outweigh the risks of clinical disease.[6] Preterm infants receiving breastmilk have lower incidences of infection, retinopathy of prematurity, and necrotizing enterocolitis than do those who receive formula, and several studies indicate that breastfeeding has a positive effect on neurodevelopmental outcomes in low birth weight infants.[6-9]

On the other hand, postnatal CMV infection negatively affects the short-term outcomes for preterm infants by increasing the risk of bronchopulmonary dysplasia (BPD) and extending hospitalizations during infancy.[10,11] There are several studies on the long-term effects of postnatal CMV infection in preterm infants. Some studies reported postnatal infection acquired early after birth via CMV-positive breast milk does not significantly affect neurodevelopment or hearing,[12-14,17] despite other reports suggesting that breastmilk-acquired CMV infection may have a detrimental influence on cognitive development in preterm infants.[15,16] However, long-term follow-up data are limited and several results were shown from studies using the same subjects. Furthermore, all previous studies evaluating the effects of postnatal CMV infection included asymptomatic infants.[12-17] Therefore, more studies are needed to better understand the long-term neurodevelopmental outcomes in infants with CMV-related symptoms.

In this report, we investigated whether there is an increased frequency of neurodevelopmental impairment in infants with CMV-related symptoms.

METHODS

The study population consisted of preterm infants (born before 32 weeks of gestation) who were admitted to Nagoya University Hospital, Japanese Red Cross Nagoya First Hospital, Toyota Memorial Hospital, Okazaki City Hospital, Tosei General Hospital, Ogaki Municipal Hospital, Anjo Kosei Hospital, and Konan Kosei Hospital between April 2004 and March 2013. A total of 250–300 VLBW infants are admitted to the neonatal intensive care unit annually at these eight institutions. Only preterm infants who were diagnosed with postnatal CMV infection during hospitalization in neonatal intensive care unit were included and their clinical records were reviewed retrospectively. Postnatal CMV infection was defined as the detection of CMV-IgM antibodies, a positive CMV antigenemia test, or CMV DNA in urine or blood[18,19] in neonates with no signs of congenital CMV infections at birth. Infants with severe congenital anomaly syndrome, congenital heart disease, or hydrops fetalis were excluded from this study. One preterm infant matched for gestational age, year of birth, and presence of intraventricular hemorrhage and periventricular leukomalacia was chosen as a control for each CMV-positive infant at each institution. intraventricular hemorrhage was diagnosed by ultrasound examinations, performed daily during the first week and then weekly, and graded according to Papile et al[20]

Periventricular leukomalacia was diagnosed by magnetic resonance imaging. BPD was defined as the need for supplemental oxygen or positive pressure support at 36 weeks of postmenstrual age. Thrombocytopenia was defined as a platelet count $< 15\times10^9/\mu L$, positive C-reactive protein was defined as C-reactive protein levels > 0.4 mg/dl, elevated liver enzyme was defined as alanine aminotransferase levels > 50 IU/dL, and hyperbilirubinemia was defined as direct bilirubin levels > 1.0 mg/dl. There was no common criteria for ganciclovir (GCV) treatment and it was decided by the attending physician at each hospital.

Neurodevelopmental outcome was evaluated at 18 months of corrected age and at 3 years of age using the Kyoto Scale of Psychological Development (KSPD) 2001. The KSPD is a standardized and widely used developmental test in Japan that correlates well with the Bayley Scales of Infant and Toddler Development, 3rd edition.[21] We defined neurodevelopmental impairment (NDI) as any of the following: a developmental quotient (DQ) of < 70 determined by the KSPD, mental retardation or cerebral palsy diagnosed by a pediatric neurologist, severe hearing impairment, or sever bilateral visual impairment.

The study was approved by the clinical research review committees of all participating hospitals. Statistical analyses were performed using the chi-square test, Fisher's exact test, or Mann–Whitney U test. $P < 0.05$ was considered statistically significant. The SPSS software package version 19 (SPSS, Chicago, IL) was used for all statistical analyses.

RESULTS

Twenty-four infants were diagnosed with postnatal CMV infection in this study period. Fourteen infants had suspected CMV infection due to sepsis-like symptoms in the absence of bacterial infection, and 10 infants had laboratory test abnormalities by regular blood examination. Twenty infants were positive for urine CMV DNA or CMV antigenemia test, and 4 infants were tested only serum CMV-IgM with positive results. The test values for CMV are shown in Table 1.

Table 1 Test values for CMV

	Number of positive patients (including duplicate data)	Median (range)
CMV DNA (blood), copies/mL	6[a]	3.9×10^3 $(5.1\times10^2–7.210^3)$
CMV DNA (urine), copies/mL	7[b]	1.9×10^5 $(6.1\times10^3–1.3\times10^7)$
CMV antigenemia, cells/1.5×10^5 leucocytes	9	4 (1–50)
CMV IgM, EU/mL	17	5.0 (1.6–10.1)[c]

CMV: cytomegalovirus

a; 3 infants with only positive results were not included

b; 6 infants with only positive results were not included

c; values of 4 infants tested only CMV-IgM were ≥4.0

Median age and postmenstrual age at onset of CMV-related symptoms were 41 days and 31 weeks, respectively. Blood examination abnormalities included thrombocytopenia (n=17; 74%), positive C-reactive protein (n=20; 82%), elevated liver enzymes (n=4; 17%), and hyperbilirubinemia (n=6; 26%). Of 24 CMV-positive infants, 17 were treated with intravenous immunoglobulin and 7 with ganciclovir (GCV). All cases treated with GCV also received intravenous immunoglobulin.

No significant differences were found in gestational age, birth weight, or the incidence of intraventricular hemorrhage or periventricular leukomalacia between the CMV-positive group and the control group (Table 2). CMV-positive infants had significantly longer hospital stays and received more home oxygen therapy after hospital discharge than did the control group, although the incidence of BPD and the duration of mechanical ventilation were not significantly different between the groups.

Table 2 Characteristics of infants in neonatal period

	CMV-positive (n = 24)	Control (n = 24)	P
Gestational age, wk	25.4 (22.7–29.9)	25.6 (23.3–30.0)	0.70
Birth weight, g	695 (389–1116)	705 (520–948)	0.41
5-min Apgar score	6 (1–9)	6 (2–10)	0.98
Intraventricular hemorrhage (IVH)	6 (25)	4 (17)	0.72
IVH grade 3–4	1 (4)	1 (4)	>0.99
Periventricular leukomalacia	1 (4)	1 (4)	>0.99
Retinopathy of prematurity treatment	18 (75)	12 (50)	0.07
Necrotizing enterocolitis	0	0	
Bronchopulmonary dysplasia	15 (63)	13 (5)	0.56
Days of mechanical ventilation	54 (0–365)	53 (0–220)	0.42
Postmenstrual age at discharge, wk	46 (39–78)	42.5 (39–66)	0.02
Body weight at discharge, g	3413 (2276–7990)	2978 (2230–6316)	0.20
Height at discharge, cm	49.5 (44.0–66.5)	47.7 (34.0–62.0)	0.10
Head circumference at discharge, cm	35.5 (33.0–43.5)	35.0 (31.0–40.2)	0.05
Home oxygen therapy	12 (50)	5 (21)	0.03
Abnormal MRI	7 (29)	10 (42)	0.37
Abnormal A-ABR	3 (13)	0	0.23

Data are presented as median (range) or n (%)

CMV: cytomegalovirus

A-ABR: automated auditory brainstem response

Neurodevelopmental outcomes at 18 months of corrected age were assessed in 21 CMV-positive infants and 23 control infants. Of those, 16 and 22 infants, respectively, were examined using the KSPD. In cases without KSPD evaluation, severe mental retardation was determined by medical examination in 3 of 5 infants in the CMV-positive group and 1 remaining infant in the control group. The incidence of NDI was not significant different between the CMV-positive and control groups (29% vs 17%). There were no significant differences in the overall DQ, any type of DQ, or anthropometric measurements between the two groups (Table 3).

Table 3 Neurodevelopmental and anthropometric outcomes at 18 months of corrected age and 3 years of age

18 months of corrected age	CMV-positive (n = 21)	Control (n = 23)	P
NDI	6 (29)	4 (17)	0.48
Overall DQ [a]	81.5 (48–102)	90 (24–102)	0.44
Postural-Motor DQ [a]	72 (30–96)	82 (27–102)	0.10
Cognitive-Adaptive DQ [a]	86.5 (67–107)	90.5 (22–107)	0.53
Language-Social DQ [a]	73.5 (48–102)	85 (23–102)	0.84
Abnormal MRI	12 (60)	11 (48)	0.54
Body weight, g	8.3 (6.4–11.2)	9.3 (6.7–10.7)	0.14
Height, cm	76.9 (70.3–81.5)	77.3 (71.3–82.4)	0.13
Head circumference, cm	45.5 (42.0–49.2)	46.2 (43.8–49.7)	0.61
3 years of age	CMV-positive (n = 21)	Control (n = 24)	P
NDI	9 (43)	7 (29)	0.34
Overall DQ [b]	77 (48–94)	79.5 (22–111)	0.46
Postural-Motor DQ [b]	76.5 (6–103)	87 (18–104)	0.21
Cognitive-Adaptive DQ [b]	76 (46–110)	77.5(25–109)	0.88
Language-Social DQ [b]	78.5 (47–101)	80.5(22–133)	0.91
Body weight, g	10.7 (8.1–13.6)	11.3 (8.3–15.0)	0.20
Height, cm	87.6 (80.8–93.2)	88.6 (80.3–93.6)	0.19
Head circumference, cm	47.4 (45.2–50.6)	49.1 (45.0–52.7)	0.11

Data are presented as median (range) or n (%)
CMV: cytomegalovirus
NDI: neurodevelopmental impairment
DQ: developmental quotient
a; CMV-positive (n=16), control (n=22)
b: CMV-positive (n=18)

Neurodevelopmental outcomes at 3 years of age were assessed in 21 CMV-positive infants and in 24 control infants. Of those, 3 CMV-positive infants were not evaluated by the KSPD and severe mental retardation was seen in all 3 of those infants by medical examination. The incidence of NDI was not significantly different between the CMV-positive group and the control group (42% vs 30%). There were no significant differences in overall DQ, any type of DQ, or anthropometric measurements between the two groups (Table 3).

We performed subgroup analyses of infants with CMV-SLS versus controls. Postural–Motor DQ at 18 months of corrected age was significantly lower in the CMV-SLS group than the control group (median [range]; 70 [44–94] vs 82 [27–102], P=0.04), but no significant difference was found at 3 years of age. Overall DQ, incidence of NDI, and anthropometric measurements were not significantly different between the two groups.

Three infants had abnormal automated auditory brainstem responses (ABR) in the neonatal period. One infant was lost for followup due to moving, one infant was re-examined by audiometry test and hearing was normal at 7 months of age, and one had a 50 dB hearing loss at 15 months of age and a 30 dB hearing loss at 3 years of age. No infants with normal automated ABR results in the neonatal period were re-examined by audiometry test after hospital discharge.

Infants with CMV-SLS were more frequently treated with GCV (6/14; 43%) than those without CMV-SLS (1/10; 10%), although it did not reach statistical significance (P = 0.10). No significant differences were found in the incidence of NDI between the groups with or without GCV at 18 months of corrected age and 3 years of age (Table 4).

Table 4 Incidence of NDI and GCV treatment

18 months of corrected age	GCV (n = 6)	no GCV (n = 15)	P
NDI, n (%)	2 (33)	4 (27)	>0.99
3 years of age	GCV (n = 7)	no GCV (n = 14)	P
NDI, n (%)	3 (43)	6 (43)	>0.99

GCV: ganciclovir
NDI: neurodevelopmental impairment

DISCUSSION

We investigated whether postnatal CMV infection adversely affects neurodevelopmental outcomes in symptomatic preterm infants and found that postnatal CMV infection did not have significant negative effects on neurodevelopmental outcomes of preterm infants at 18 months of corrected age and at 3 years of age. This finding is consistent with the results of several previous studies including the recent largest one.[12-14,17]

About half of infants with postnatal CMV infection in the preterm period are asymptomatic.[5] All CMV-positive infants in this study had some CMV-related symptoms, suggesting that these infants had more severe cases than those in previous studies evaluating neurodevelopmental outcomes, all of which included asymptomatic infants.[12-16] Our results thus suggest that postnatal CMV infection does not have significant adverse effects on neurodevelopmental outcomes up to 3 years of age, even in relatively severe cases. However, we also showed that Postural–Motor DQ at 18 months of corrected age was significantly lower in infants with CMV-SLS than in the control group. In addition, the incidence of NDI was higher and any type of DQ was lower in the CMV-positive group than in controls, although differences were not significant. Infants without KSPD evaluation due to severe mental retardation were more commonly seen in the CMV-positive group than in the control group, suggesting the differences in DQ between the two groups might have been higher if these infants had been evaluated with this test as well. Some studies suggested that acquired CMV infection had a detrimental effect on neurodevelopment of preterm infants.[15,16] Bevot et al reported that significant differences between CMV-positive and CMV-negative infants were found for both motor and cognitive function, with poorer performance in the CMV-positive group at school age, though their values were within the normal range.[16] There is a possibility that significant differences appear when the children get older, so long-term follow-up data will be needed in our study participants.

Preterm infants who were fed breast milk from CMV-seropositive mothers are at risk for postnatal CMV infection; though, transmission rate varied according to the report.[5,22,23] Nevertheless, breast milk provides many benefits to premature infants. In the 2012 policy statement on breast feeding and use of human milk, the American Academy of Pediatrics stated, "The value of routinely feeding human milk from seropositive mothers to preterm infants outweighs the risks of clinical disease, especially because no long-term neurodevelopmental abnormalities have been reported."[6] Our study supports this statement at this moment.

One study reported that postnatal CMV infection was associated with an increased risk for BPD.[10] In this study, the incidence of BPD was not significantly different between the CMV-positive group and the control group, but home oxygen therapy was administered significantly more often in the former group. In addition, CMV-positive infants had significantly longer hospital stays. Therefore, our study, as well as other studies, indicates that postnatal CMV infection impairs short-term outcomes in preterm infants.

No controlled study has yet evaluated the impact of antiviral treatment on the outcome of postnatally acquired CMV infection, and no treatment recommendations have emerged so far. Fischer et al reported that the clinical course of severe postnatal CMV infection in extremely low birth weight infants was rapidly improved after intravenous GCV.[24] We did not show that GCV treatment had an effect on long-term outcome. However, the criteria for GCV treatment were not determined in this study and attending physicians used GCV at their own discretion. In addition, GCV was used more often in infants with CMV-SLS than in those without CMV-SLS. Therefore, in this study, we did not sufficiently evaluate the effectiveness of GCV treatment for postnatal CMV infection.

The small number of diagnosed cases of CMV infection was one of the limitations of this study. In the participating institutions of this study, the policy was to feed frozen breast milk to preterm infants. Among infants who were fed frozen breast milk from CMV-seropositive mothers, 3–14% had CMV-related symptoms.[5] In Japan, CMV seroprevalence in women of childbearing age were reported at 67% in a recent study.[25] Based on these results, it was estimated that approximately 50 to 280 VLBW infants would be infected and have CMV-related symptoms in the participating institutions during the study period. However, postnatal CMV infection was confirmed in only 24 infants in this study; this suggests that many CMV-infected infants may not have been examined on suspicion of CMV infection and were therefore not diagnosed.

Our study had several additional limitations. First, we were not able to exclude cases of congenital infection from the group of CMV-positive infants by virological methods. To rule out congenital CMV infections is difficult in normal practice, as the tests for CMV are not carried out during the first few weeks of life unless congenital infection is suspected. However, we believe the possibility that our group contained congenitally infected infants was extremely low because the enrolled infants did not have features of congenital CMV infection, and the prevalence of congenital CMV infection itself is extremely low, about 0.3%. Second, we were not able to examine the outcomes of preterm infants based on the routes of CMV infection. Breastfeeding is a main route for CMV transmission during the first year of life, and all participating institutions tried to use CMV-IgG seronegative blood products when an infant needed a blood transfusion. Therefore, we are confident that almost all, if not all, infected cases were transmitted through breast milk. To the best of our knowledge, no studies have investigated the outcome of preterm infants with CMV transmission through blood products. Third, although control infants were matched with CMV-positive cases by gestational age, year of birth, and the presence of intraventricular hemorrhage and periventricular leukomalacia, it was not confirmed that they did not acquire CMV infection during the perinatal period. However, these infants were selected from the same institution close to the same time as the infected infants, so examinations and treatments were completed using the same methods/protocols for intensive and/or routine care for VLBW infants. Forth, false positives for serum IgM to CMV infection are occasionally present. However, the 4 infants diagnosed by only positive serum IgM were associated with abnormal blood test results or infectious symptoms. Therefore, we consider them to have CMV infection. Finally, because of the small sample size, there is a possibility that this study did not have enough power to show significant differences.

In conclusion, postnatal CMV infection did not have a significant negative influence on

neurodevelopmental outcomes of symptomatic preterm infants at 18 months of corrected age and at 3 years of age in this study. However, the incidence of NDI was higher and all types of DQ were lower in the CMV-positive group than in the control group. Larger studies with long-term follow-up are needed for a better understanding of continued neurodevelopmental outcomes in preterm infants with postnatal CMV infection.

CONFICT OF INTEREST

The authors declare that they have no conflict of interest.

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