Outcome of Preterm Infants With Postnatal Cytomegalovirus Infection

Julia Gunkel, MD, PhD,[a] Linda S. de Vries, MD, PhD,[a] Marian Jongmans, PhD,[a,b] Corine Koopman-Esseboom, MD, PhD,[a] Ingrid C. van Haastert, MA, PhD,[a] Maria C.J. Eijsermans, MSc,[c] Carolien van Stam, MSc,[d] Bert G.A. van Zanten, PhD,[e] Tom F.W. Wolfs, MD, PhD,[f] Joppe Nijman, MD, PhD[a]

abstract

OBJECTIVES: To assess whether preterm infants with postnatal cytomegalovirus infection develop neurologic sequelae in early childhood.

METHODS: Infants <32 weeks' gestation were prospectively screened for cytomegalovirus (CMV) at term-equivalent age. Neurodevelopment was compared between CMV-positive and CMV-negative infants by using the Griffiths Mental Development Scales (GMDS) at 16 months' corrected age (CA); the Bayley Scales of Infant and Toddler Development, Third Edition or the GMDS at 24 to 30 months' CA; and the Wechsler Preschool and Primary Scale of Intelligence, Third Edition and Movement Assessment Battery for Children, Second Edition at 6 years of age. At 6 years old, hearing was assessed in CMV-positive children.

RESULTS: Neurodevelopment was assessed in 356 infants at 16 months' CA, of whom 49 (14%) were infected and 307 (86%) were noninfected. Infected infants performed significantly better on the GMDS locomotor scale. There were no differences at 24 to 30 months' CA on the Bayley Scales of Infant and Toddler Development, Third Edition or GMDS. At 6 years of age, infected children scored lower on the Wechsler Preschool and Primary Scale of Intelligence, Third Edition, but mean scores were within normal range, reaching significance only in verbal IQ (96 [SD 17] vs 103 [SD 15] points; $P = .046$). Multiple regression indicated no impact of CMV status but significant influence of maternal education and ethnicity on verbal IQ. No significant differences in motor development were found and none of the infected children developed sensorineural hearing loss.

CONCLUSIONS: In this cohort study, postnatal cytomegalovirus infection in preterm children did not have an adverse effect on neurodevelopment within the first 6 years of life.

Departments of [a]Neonatology, [b]Child, Family, and Education Studies, [d]Pediatric Psychology and Social Work, [e]Ear, Nose, and Throat and Audiology, and [f]Pediatric Infectious Diseases, and [c]Child Development and Exercise Center, University Medical Center Utrecht, Utrecht, Netherlands

Dr Gunkel was responsible for data collection and analysis, drafted the manuscript, and reviewed and finalized the manuscript; Drs de Vries, Jongmans, Koopman-Esseboom, van Haastert, Eijsermans, and van Stam conducted part of the neurodevelopmental testing and critically reviewed the manuscript; Dr van Zanten conducted the audiological testing at 6 years of age and reviewed the manuscript; Dr Wolfs critically reviewed the manuscript; Dr Nijman was responsible for data collection and analysis, manuscript drafting, and critically reviewed the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Address correspondence to Joppe Nijman, MD, PhD, Department of Neonatology, University Medical Center Utrecht, House-post KE 04.123.1, Postbus 85090, 3508AB, Utrecht, Netherlands. E-mail: j.nijman@umcutrecht.nl

WHAT'S KNOWN ON THIS SUBJECT: Postnatal cytomegalovirus (pCMV) infection is most frequently transmitted through fresh breast milk. Despite its benefits, breast milk is frequently withheld or pretreated to avoid virus transmission to preterm infants. The effects of a pCMV infection on neurodevelopment are insufficiently studied.

WHAT THIS STUDY ADDS: This study does not show an adverse effect of pCMV infection on neurodevelopment, including hearing in infancy and early childhood. Therefore, measures to withhold fresh breast milk in the neonatal period may not be warranted.

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Postnatal cytomegalovirus (pCMV) infection is a common viral infection and frequently affects preterm infants (gestational age [GA] <32 weeks) and very low birth weight (VLBW) (birth weight <1500 g) infants, with an estimated median incidence of 20%.[1,2] cytomegalovirus (CMV) is mainly transmitted via CMV-seropositive mothers shedding the virus in their breast milk, of whom ~37% to 76% will transmit the virus to their infants.[3,4] Whereas term infants are asymptomatic, preterm infants and VLBW infants may be at risk for symptomatic disease.[5,6] Symptomatic disease, such as CMV-related sepsislike syndrome (SLS), thrombocytopenia, pneumonia, and/or hepatitis, may occur but is rare (median incidence 4%).[1,5,7] CMV is the leading nongenetic cause of sensorineural hearing loss (SNHL).[8] SNHL was not found in infants with pCMV infection at 2 years[9] and 8 years of age.[10] Data on the neurodevelopmental outcomes of children with pCMV infection are scarce and limited to small-cohort studies. In preterm infants, neurodevelopment until 4 years of age appears to be within the normal range.[10–12] However, researchers in several studies have suggested a negative impact on cognitive development at school age.[13–15] Because of the uncertainty regarding the short- and long-term consequences of a pCMV infection, fresh, untreated breast milk is not always given to VLBW infants.[16–18] Because (untreated) breast milk is known to improve infant health,[19] it is important to study the effects of pCMV infection in a large cohort of preterm infants. Our aim in this prospective, longitudinal cohort study is to examine the consequences of a pCMV infection on neurodevelopmental outcomes, including hearing, in a cohort of preterm infants until 6 years of age.

METHODS

Study Population

From April 2007 until December 2010, all infants <32 weeks GA admitted to the level 3 NICU of the Wilhelmina Children's Hospital in Utrecht, the Netherlands, were screened for CMV, predominantly with urine obtained at term-equivalent age (TEA) (40 weeks postconceptional age) during a routine follow-up visit at the outpatient clinic by using CMV polymerase chain reaction (PCR) as previously described.[6] Congenital CMV infection was excluded by a negative CMV-PCR result on urine collected within 1 week after birth.[6] Exclusion criteria were as follows: absence of urine at TEA, severe cerebral abnormalities (ie, porencephalic cyst, cystic periventricular leukomalacia, posthemorrhagic ventricular dilatation requiring the insertion of a ventricular reservoir or ventriculoperitoneal shunt, or intraventricular hemorrhage [IVH] grade III and IV), chromosomal anomalies, death before TEA, and no parental consent. For the analysis of neurodevelopmental outcomes at 6 years old, only children with a GA of ≤30 weeks were included. The internal review committee of our hospital approved this study.

Case Definitions

Clinical and demographic characteristics were collected as previously described.[6] Additionally, small for gestational age (SGA) status, socioeconomic status (SES), and maternal education were recorded. SGA was defined as birth weight by GA <10th percentile. Percentiles for our population were obtained from the Dutch perinatal registry.[20] SES was determined indirectly by using the SES of the parent's postal code and was provided by The Netherlands Institute for Social Research.[21] A score <−1 was considered low, between −1 and 1 was average, and >1 was high. Symptoms of pCMV disease included SLS, pneumonia, cholestasis, and/or thrombocytopenia.[5] Criteria for a diagnosis of symptomatic CMV disease were the presence of SLS, pneumonia, and cholestasis.[6] During admission to the NICU and at TEA, cranial ultrasonography was performed as previously described.[6]

Neurodevelopmental Assessment

Neurodevelopmental outcome was routinely assessed by developmental specialists at the outpatient clinic by using the Griffiths Mental Development Scales (GMDS)[22] at 16 months' corrected age (CA) and the Bayley Scales of Infant and Toddler Development, Third Edition (BSITD-III)[23] at 24 to 30 months' CA. The BSITD-III was routinely used in infants <30 weeks GA at 24 to 30 months. When infants had a higher GA (30–32 weeks), the GMDS was used instead. At 6 years of age, all preterm infants ≤30 weeks GA received a routine general pediatric assessment that included motor function using the Movement Assessment Battery for Children, Second Edition (MABC-II).[24] Cognitive function was routinely assessed at our hospital by using the Wechsler Preschool and Primary Scale of Intelligence, Third Edition (WPPSI-III)[25] for all children born ≤28 weeks GA. Children born >28 weeks GA who have abnormal development at 6 years old are only tested with the WPPSI-III at the request of the pediatrician. Therefore, inclusion numbers are lower for the WPPSI-III than for the MABC-II (Fig 1). All eligible infants with a pCMV infection and >28 weeks GA were tested by using the WPPSI-III as part of this study. A detailed account of the GMDS, BSITD-III, MABC-II, and WPPSI-III has been previously described.[26,27] For the GMDS and BSITD-III, *z* scores were calculated to compare outcome at 2 years of age. Both the GMDS and BSITD-III scores were corrected for preterm birth. When the BSITD-III was administered at 24 months' CA, parents were asked to provide the age of onset of independent walking (AOIW), which was defined as walking at least 5 steps independently.[23]

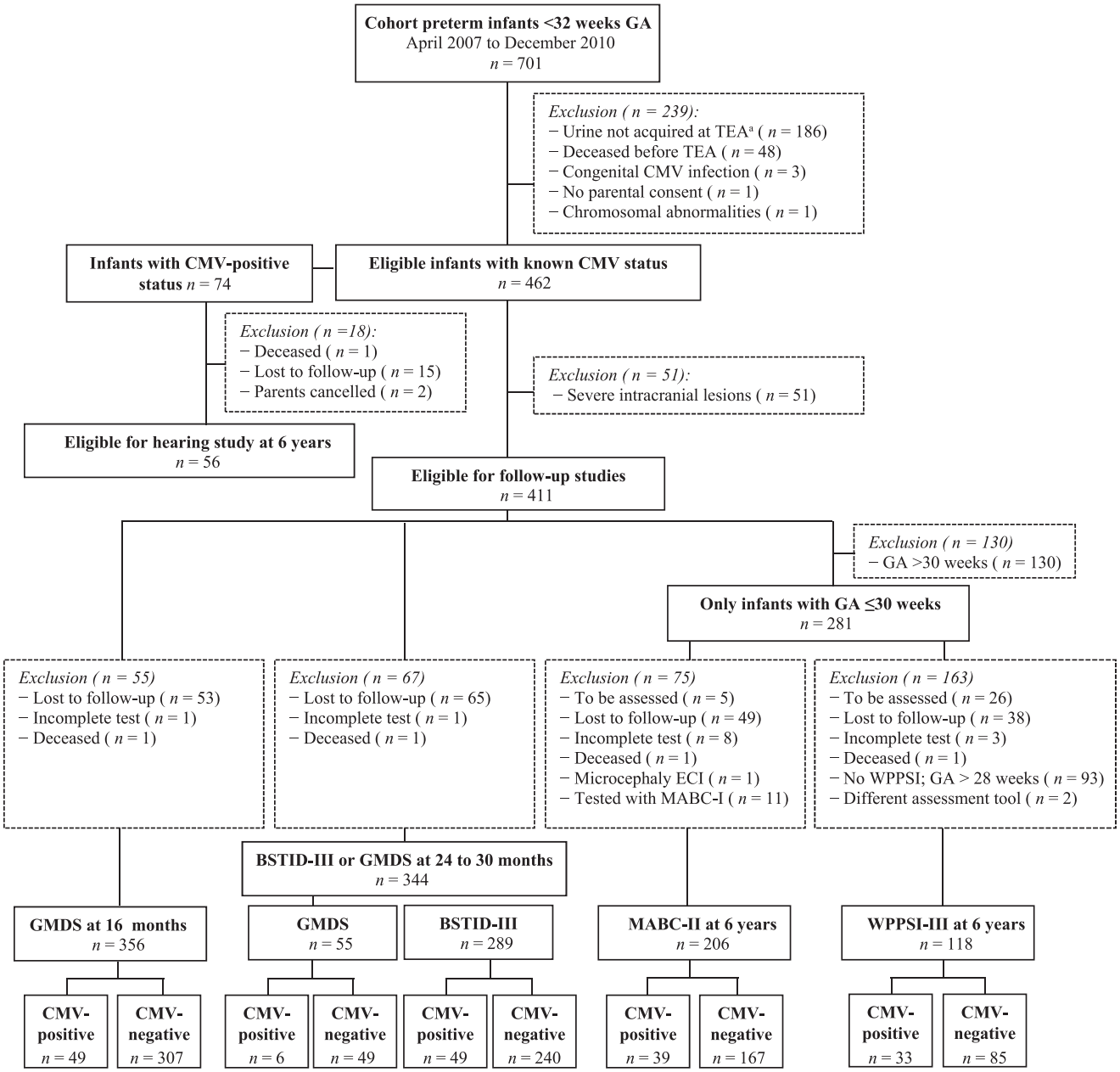

FIGURE 1
Inclusion of study population. [a] TEA: term-equivalent age (40 weeks postconceptional age).

Hearing Assessment

At 6 years of age, all children with a pCMV infection underwent pure tone audiometric testing with headphones, following standardized procedures in a tertiary-care audiology center.

When pure tone audiometric testing was not feasible because of patient incompliance, behavioral observation audiometry was used instead. Pure tone–averaged (500, 1000, 2000, and 4000 Hz) hearing loss was calculated for each ear. Audiograms were assessed for conductive or SNHL. Speech performance curves were measured by using the standardized Dutch consonant-vowel-consonant list for children[28] and assessed for the maximum speech discrimination score and curve displacement (>20 dB from the reference curve). Middle-ear function was assessed by impedance audiometry. The degree of hearing impairment was classified according to the World Health Organization grading system.[29] SNHL was defined as a threshold elevation of >25 dB without any component of conductive hearing loss.

Statistical Analysis

Statistical analysis was performed by using IBM SPSS Statistics version 23 (IBM Corporation). Figures were

produced in GraphPad Prism version 5.03 (GraphPad Software Inc, La Jolla, CA). Categorical and dichotomous variables were analyzed by using the χ^2 test. Continuous variables were analyzed with 2-tailed Student's *t* tests. One-way analysis of variance was used to determine correlations among continuous variables. A *P* value of <.05 was considered statistically significant. Multiple-regression analyses were performed with AOIW and subsets of the WPPSI-III as dependent variables and pCMV infection and significantly correlated parameters as independent variables.

RESULTS

Study Population

During the study period, CMV status at TEA could be determined in 462 of 701 (66%) preterm infants <32 weeks GA, of whom 411 (89%) were eligible for follow-up (Fig 1). CMV status could not be determined in 186 of 701 (27%) infants because the collection of urine at TEA was not successful. A pCMV infection was diagnosed in 74 infants; congenital CMV infection was excluded in 63 (85%) by using a CMV-PCR of the urine collected in the first week and in 11 (15%) by using CMV-PCR combined with anti-CMV immunoglobulin-M analysis of dried blood spots cards. Of the 74 infected infants, 56 (76%) could be included in the hearing study. Clinical symptoms of CMV-disease were observed in 4 of 74 (5%) infants and included thrombocytopenia (*n* = 1), pneumonia (*n* = 2), and SLS with pneumonia and thrombocytopenia (*n* = 1). One infant with symptomatic pCMV infection died at 6 months of age because of severe prematurity–related respiratory problems present since birth and before the pCMV infection. None of the infants were treated with Valganciclovir or Ganciclovir because all symptoms were self-limiting.[5] All CMV-positive infants were exclusively fed fresh breast milk from their mothers. Clinical and demographic data with respect to CMV status are summarized in Table 1 for infants who were tested at 24 to 30 months and for children who were tested at 6 years of age. The clinical characteristics of infants who were assessed at 16 months were comparable with infants who were assessed at 24 to 30 months (data not shown). Baseline characteristics of the infants who were tested with the WPPSI-III at 6 years of age can be found in Supplemental Table 3. Baseline characteristics of the children who received hearing assessment at 6 years of age can be found in Supplemental Table 4. Overall, infected infants were significantly more often born to mothers of non-Western origin, were fed fresh breast milk more frequently, and had lenticulostriate vasculopathy (LSV) at TEA more frequently (Table 1). These findings have been previously reported.[6]

GMDS at 16 Months

A total of 49 of 356 (14%) infants with a pCMV infection and 307 of 356 (86%) noninfected infants were tested at a mean age of 16.4 months' CA (SD 1.8) and 16.1 months' CA (SD 1.3), respectively. The mean locomotor subscale quotient was significantly higher in infants with a pCMV infection (*z* score 0.35 [SD 0.81] vs 0.02 [SD 0.98] in the control group, which corresponds to a quotient of 102 [SD 12] vs 97 [SD 14]; *P* = .025; Fig 2A). Other subscales did not differ significantly. The mean general developmental quotient was comparable in infected and noninfected infants (102 [SD 9] vs 101 [SD 9], respectively; *P* = .320) and was within the normal range.

GMDS or BSITD-III at 24 to 30 Months

A total of 49 of 289 (17%) infants with a pCMV infection and 240 of 289 (83%) noninfected infants were tested by using the BSITD-III at a mean age of 26.1 months' CA (SD 3.0) and 25.3 months' CA (SD 2.5), respectively. In 6 of 55 (11%) infected infants and 49 of 55 (89%) noninfected infants, the GMDS was used instead at a mean age of 23.1 months (SD 1.2) and 24.6 months (SD 1.7), respectively. There were no significant differences in BSITD-III and GMDS *z* scores between infected and noninfected infants (Fig 2B and 2C, respectively). The mean corrected cognitive composite scores and total motor composite score in infected and noninfected infants by using the BSITD-III at 24 months (104 [SD 10] vs 105 [SD 12], respectively; *P* = .184; 109 [SD 10] vs 109 [SD 12], respectively; *P* = .748) were within the normal range.

AOIW

The mean AOIW was compared between 49 infants with a pCMV infection and 239 noninfected infants. Postnatally infected infants were able to walk at a younger CA compared with noninfected infants (14.7 months [SD 2.4] and 15.8 months [SD 3.1], respectively; *P* = .026). Multiple regression analysis showed that significantly earlier AOIW was related to non-Western maternal origin (NWMO) (Supplemental Table 5). The mean AOIW was 14.1 months (SD 2.8) in infants of mothers of non-Western ethnicity compared with a mean AOIW of 16.0 months (SD 3.0) in infants of mothers of Western ethnicity (*P* < .001).

WPPSI-III at 6 Years of Age

In total, 33 of 118 (28%) children with a pCMV infection and 85 of 118 (72%) noninfected children were tested at a mean age of 5.7 years (SD 0.3) and 5.7 years (SD 0.5), respectively. Mean scores were in the normal range on all 4 domains for infected and noninfected children, but infected children had overall lower scores (Table 2). This only reached statistical significance on the subscale of verbal IQ (96 [95% confidence interval (CI) 90 to 102] vs 103 [95% CI 100 to 106]; *P* = .046). Multiple-regression analyses indicated that the presence of respiratory distress syndrome (RDS) significantly impacted total IQ (coefficient −5.9;

TABLE 1 Clinical and Demographic Characteristics of Preterm Infants Assessed With the BSITD-III or GMDS at 24 Months' CA and/or 6 Years of Age With the WPPSI-III and/or the MABC-II With Respect to pCMV Infection

	Infants Assessed at 24 mo CA (GA <32 wk)		*P*	Infants Assessed at 6 y (GA ≤30 wk[a])		*P*
	CMV-Positive (*n* = 55)	CMV-Negative (*n* = 289)		CMV-Positive (*n* = 41)	CMV-Negative (*n* = 172)	
Clinical and demographic characteristics						
GA, mean, wk, (range)	28.2 (24.3–31.3)	28.8 (24.7–31.9)	.022	27.7 (24.3–30)	28 (24.4–30)	.242
Birth wt, mean, g (SD)	1129 (287)	1181 (319)	.261	1076 (266)	1074 (257)	.964
SGA, *n* (%)	5 (13)	39 (14)	.803	1 (2)	16 (9)	.145
Male sex, *n* (%)	31 (56)	157 (54)	.781	23 (56)	83 (48)	.367
NWMO, *n* (%)	30 (55)	42 (15)	<.001	25 (61)	21 (12)	<.001
Apgar score at 1 min, mean (SD)	7 (2)	7 (2)	.231	7 (2)	6 (2)	.463
Apgar score at 5 min, mean (SD)	8 (2)	8 (1)	.592	8 (1)	8 (1)	.965
Breast milk, *n* (%)	55 (100)	229 (79)	<.001	41 (100)	137 (80)	.002
RDS, *n* (%)	22 (40)	150 (52)	.106	19 (46)	112 (65)	.026
>7 d mechanical ventilation, *n* (%)	3 (6)	45 (16)	.047	2 (5)	31 (18)	.037
Chronic lung disease, *n* (%)	1 (2)	16 (6)	.244	1 (2)	14 (8)	.200
PDA, *n* (%)	12 (22)	71 (25)	.662	10 (24)	51 (30)	.503
Surgery for PDA, *n* (%)	2 (4)	10 (4)	.948	2 (5)	7 (4)	.817
Hypotension treated with inotropes, *n* (%)	11 (20)	105 (36)	.019	6 (15)	72 (42)	<.001
No. transfusions, median (range)	1 (0–15)	1 (0–18)	.881	2 (0–15)	2 (0–18)	.598
Sepsis, *n* (%)	13 (24)	94 (33)	.192	8 (20)	59 (34)	.067
Necrotizing enterocolitis, *n* (%)	0	9 (3)	.185	0	6 (4)	.225
NICU admission d, mean (SD)	33 (21)	34 (24)	.890	38 (21)	41 (24)	.435
SES						
Low, *n* (%)	12 (22)	35 (12)	.055	11 (27)	19 (11)	.009
Average, *n* (%)	34 (62)	192 (66)	.508	23 (56)	116 (67)	.170
High, *n* (%)	9 (16)	62 (22)	.393	7 (17)	37 (22)	.528
Cranial ultrasonography findings						
IVH (%)						
Grade I, *n* (%)	5 (11)	29 (14)	.576	5 (12)	20 (12)	.919
Grade II, *n* (%)	6 (13)	27 (13)	.996	4 (10)	24 (14)	.475
LSV at TEA, *n* (%)	20 (36)	49 (17)	.001	15 (37)	34 (20)	.021
Germinolytic cysts at TEA, *n* (%)	5 (15)	12 (13)	.729	5 (12)	25 (15)	.699

PDA, patent ductus arteriosus.

[a] GA of 30 completed weeks or less.

P = .046) and verbal IQ (coefficient −8.8; *P* = .004; Supplemental Table 6). NWMO (coefficient −7.7; *P* = .049) and low maternal education (coefficient −8.3; *P* = .019) also significantly impacted verbal IQ. CMV was not significantly associated with impaired outcomes on any of the 4 WPPSI-III domains. No significant differences were found between symptomatic and asymptomatic children (Supplemental Tables 7 and 8).

MABC-II at 6 Years of Age

Thirty-nine (19%) children with a pCMV infection and 167 (81%) noninfected children were tested at a mean age of 5.8 years (SD 0.2) and 5.7 years (SD 0.4), respectively (*P* = .155). There were no significant differences in the median scores of the MABC-II subscales between both groups (Table 2). The median total impairment standard score between infected children and noninfected children was 8 points and 9 points (*P* = .661), respectively, and was in the normal range.

Hearing Outcome at 6 Years of Age in Children With pCMV Infection

Seventy-four (16%) children had a pCMV infection, of whom 56 (76%) were audiologically tested at a mean age of 5.8 years (SD 0.2; Fig 1). None of the children had SNHL. Pure tone audiometry was conducted in all children. Forty-four (79%) children had normal hearing. A slight hearing impairment (26–40 dB) was seen in 9 (16%) children, of whom 7 had unilateral conductive hearing loss and 2 had bilateral conductive hearing loss. Tympanometry indicated middle-ear dysfunction in all of them (middle-ear fluid, *n* = 2; negative pressure in the middle-ear cavity, *n* = 5; middle-ear fluid and negative pressure in the middle-ear cavity, *n* = 2). A moderate impairment (41–60 dB) was seen in 3 (5%) children, of whom 1 had unilateral conductive hearing loss and 2 had bilateral conductive hearing loss.

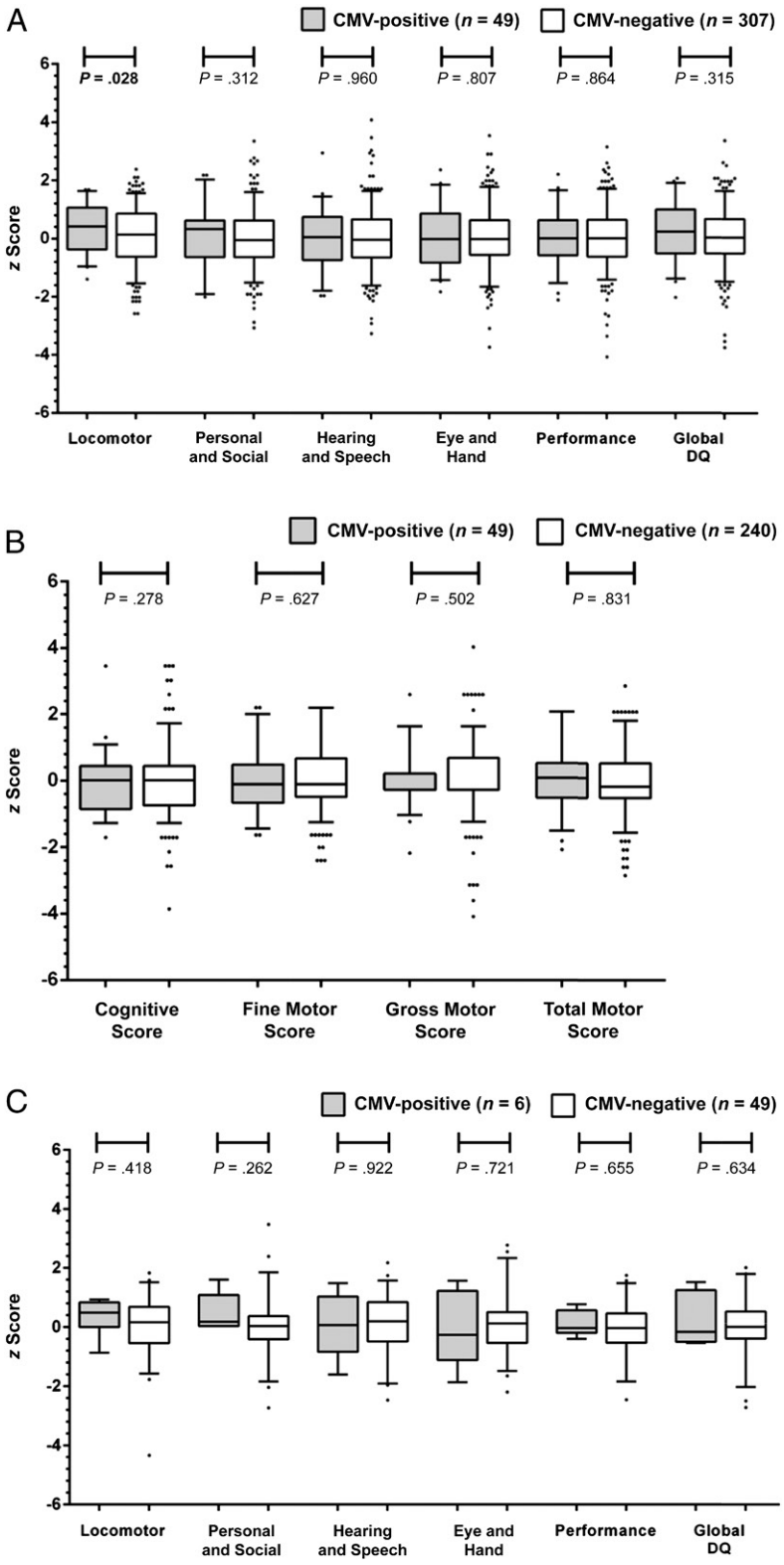

FIGURE 2

A, *z* score of the GMDS at 16 months' CA. B, *z* score of the BSITD-III at 24 months' CA. C, *z* score of the GMDS at 30 months' CA. The upper and lower borders of the box plots represent the 25th and 75th percentiles; bars represent median *z* scores, and whiskers represent the 5th and 95th percentiles. Outliers are depicted as dots.

Again, tympanometry indicated middle-ear dysfunction in all children (middle-ear fluid, $n = 1$; negative pressure in the middle-ear space, $n = 1$; cholesteatoma and negative pressure in the middle-ear space, $n = 1$). Speech audiometry was conducted in 2 children and reflected the conductive moderate impairment seen on pure tone audiometry. Cochlear function was normal in all the tested children.

DISCUSSION

To the best of our knowledge, this is the largest prospective cohort study in which researchers examine neurodevelopmental outcomes of preterm infants with a pCMV infection from birth until early childhood. The results of this study did not show an impaired neurodevelopmental outcome (including SNHL) until 6 years of age in preterm infants with a pCMV infection. So far, outcome studies were inconclusive in terms of the long-term effects of a pCMV infection in preterm infants. Although short-term development until 2 to 4.5 years of age seems to be unaffected,[11,12,30] more recently, smaller case-controlled studies managing infected children until school age and into adolescence have shown subtle impairments in cognitive functioning when compared with uninfected controls.[10,13,14,31] In line with previous studies on short-term outcomes,[11,12,30] we did not find any adverse neurodevelopmental sequelae in 55 preterm infants with a pCMV infection compared with 289 noninfected infants until 2 years' CA. Cognitive assessment at 6 years of age indicated slight discrepancies between the groups. Overall, infected children scored in the normal range but had lower mean scores on all domains, reaching significance on the domain of verbal IQ only. CMV status did not significantly contribute to the observed variance on any subscales of the WPPSI-III. NWMO and low maternal education were significantly associated with a lower verbal IQ score.

TABLE 2 Results of the WPPSI-III and MABC-II at 6 Years of Age

Measure			*P*
WPPSI-III	CMV-positive (*n* = 33)	CMV-negative (*n* = 85)	
Total IQ, mean (95% CI)[a]	96 (91 to 101)	101 (98 to 104)	.079
Verbal IQ, mean (95% CI)	96 (90 to 102)	103 (100 to 106)	.046
Performance IQ, mean (95% CI)	100 (95 to 105)	102 (99 to 105)	.456
Processing speed quotient, mean (95% CI)[b]	92 (86 to 98)	93 (90 to 96)	.708
MABC-II	CMV-positive (*n* = 39)	CMV-negative (*n* = 167)	
Total impairment score, median (range)[a]	8 (4–14)	9 (2–15)	.661
Manual dexterity, median (range)	8 (4–14)	9 (2–15)	.902
Aiming and catching ball skills, median (range)	10 (5–17)	9 (1–15)	.052
Dynamic and static balance, median (range)[a]	8 (4–16)	9 (2–17)	.081

[a] Data from 1 child missing.
[b] Data from 6 children missing.

NWMO has been previously identified as a risk factor for pCMV acquisition,[6] and children with pCMV infection in this study had significantly more mothers of non-Western ethnicity.[5] It is conceivable that children whose parents do not speak Dutch as their first language may learn the native languages and differing cultural norms of their parents' ethnic backgrounds first.[32,33] As such, the WPPSI-III, which is conducted in Dutch at our institution, may pose a cultural and/or language barrier to these children. The occurrence of pCMV infection and low verbal IQ may not be causal but rather unrelated occurrences associated with social and epidemiologic factors. Several long-term, developmental outcome studies of children with a pCMV infection reported similar cognitive results at 6 and 8 years of age.10,[13] In contrast to our results, however, in the study by Bevot et al,[10] pCMV infection contributed independently to lower scores on all cognitive subscales and, in combination with paternal SES, on the overall cognitive composite score at 8 years of age. Interestingly, in the study by Goelz et al,[13] which included the cohort of Bevot et al,[10] the significant cognitive differences initially observed were not confirmed. Similar to our study, low SES (consisting also of parental education) significantly contributed to the overall lower cognitive scores. The absolute contribution of CMV status on outcomes was not reported. It has been suggested that the effects of an early pCMV infection may only manifest at school age and/or adolescence, a time when complex, higher cognitive functions develop.[14] In the most recent study by Brecht et al,[14] infected adolescents (11–17 years of age) had significantly lower general intelligence scores than noninfected preterm and term adolescents, findings that could not be explained by differences in maternal education, attention, or brain pathology. An important confounder not controlled for in the study by Brecht et al[14] is parental ethnicity. Lower maternal education and an immigrant background of both parents have been linked to an impaired long-term composite IQ at 10 to 13 years of age.[34]

Researchers in a recent study observed an increased occurrence of bronchopulmonary dysplasia in VLBW infants with a pCMV infection.[35] In the current study, the development of bronchopulmonary dysplasia was similar in both groups, in contrast to the findings by Kelly et al,[35] most likely because of methodological differences in study design. Selection bias may have confounded the results of Kelly et al[35] because they were not weighed against a population of asymptomatic VLBW infants with a pCMV infection; therefore, these results should be interpreted with caution. In our population studied at 6 years of age, the control group had significantly more RDS and mechanical ventilation for >7 days. RDS independently contributed to a lower total IQ and verbal IQ, but still the control group attained a higher score compared with infected infants. It is possible that the differences in scores between the groups would have been more pronounced without baseline differences in neonatal morbidity (including RDS).

In terms of motor development, infected infants had better gross motor performance at 16 months' CA and had significantly earlier AOIW. We analyzed the association between pCMV infection and AOIW for possible confounders and found that NWMO ethnicity had a positive effect on independent walking. Ethnicity has previously been associated with AOIW in a study on AOIW in Dutch preterm infants.[36] At 6 years of age, all median scores were in the normal range, without significant differences on all subscales of the MABC-II. We have previously demonstrated microstructural changes in the occipital white matter of infants with a pCMV infection.[37] Although no visual assessment was conducted, infected children actually scored better than noninfected children on ball skills when using the MABC-II at 6 years of age. The significance of these microstructural changes remains to be elucidated. Previously and in the current study, we have shown that LSV not yet present at birth is more common in preterm infants with a pCMV infection.[6] LSV is not pathognomonic for CMV infections, and

the exact causal relationship between pCMV infection and the occurrence of LSV remains unclear.[38] Previous studies in infants with a pCMV infection have reported an association between pCMV infection and the presence of LSV.[39,40] In this study, LSV was not associated with impaired neurodevelopmental outcome at 2 years' CA and at 6 years of age.

SNHL is a well-known sequela of pCMV infection[8] but has so far not been detected in infants with a pCMV infection.[5] At 12 and 24 months, SNHL has been previously excluded for this cohort.[9] At 6 years of age, despite the presence of conductive hearing loss among 12 children, none of the infected children developed SNHL.[12]

This study has several limitations, most important of them being that we did not determine the onset of CMV infection, and therefore, we cannot exclude that an early pCMV infection may still have detrimental effects on neurodevelopment. The timing of CMV acquisition and subsequent first viral detection in relation to birth weight and GA seem to be the most important risk factors for symptomatic CMV disease.[7,41,42] In this study, of the infants with a pCMV infection assessed at 6 years of age ($n = 33$), 9% ($n = 3$) were symptomatic in the neonatal period. No significant difference was noted between symptomatic and asymptomatic infants (Supplemental Tables 7 and 8). Because so few infants were symptomatic, no conclusions can be made about the impact of clinical symptoms on outcomes. In the subgroup of noninfected infants >28 weeks GA, selection bias may have been introduced because the WPPSI-III was performed at the discretion of the pediatrician. This selection may have had a negative effect on the WPPSI-III scores. Nevertheless, WPPSI-III scores in this subgroup were within the normal range of the population (data not shown). Furthermore, there was the common issue of loss to follow-up in long-term, prospective follow-up studies, which may have introduced selection bias. More prospective cohort studies are needed whereby the timing of virus acquisition and symptomatic disease are correlated with long-term neurodevelopmental outcomes. Despite the unsuccessful collection of urine among 27% of the infants during visits to the outpatient clinic at TEA, a comparative analysis at baseline did not show any statistically significant differences compared with the included infants.

The results of the current study, in which no obvious deleterious effect of pCMV infection on neurodevelopmental outcomes in early childhood has been shown, may not justify interventions like pasteurization or freezing or withholding breast milk to prevent CMV transmission in the general preterm population.

Different feeding policies have been observed in NICUs among several European countries whereby mothers are often routinely tested for CMV serostatus, and, if positive, the breast milk is pretreated, formula is given,[18] or routine, standard freezing of all breast milk for infants <32 weeks GA is performed.[16] In extremely preterm and VLBW infants, however, CMV may act as an aggravator of an already fragile system, causing symptomatic infection.[5,7] These infants may benefit from a delayed introduction of breast milk or pretreatment of breast milk to prevent a symptomatic pCMV infection[5] until the exact long-term consequences are determined.

CONCLUSIONS

The neurodevelopmental outcomes of children with a pCMV infection was within the normal range in early childhood. At 6 years of age, infected children had lower cognitive scores, with only a significant difference in verbal IQ, which could be attributed to maternal education and ethnicity and not CMV status. Median motor function at 6 years of age was within the normal range. None of the infected children developed perceptive hearing loss. More prospective cohort studies are needed to examine cognitive development in extremely preterm infants (GA <26 weeks) to determine the consequences of early and/or symptomatic pCMV infection.

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ABBREVIATIONS

AOIW: age of onset of independent walking
BSITD-III: Bayley Scales of Infant and Toddler Development, Third Edition
CA: corrected age
CI: confidence interval
CMV: cytomegalovirus
GA: gestational age
GMDS: Griffiths Mental Development Scales
IVH: intraventricular hemorrhage
LSV: lenticulostriate vasculopathy
MABC-II: Movement Assessment Battery for Children, Second Edition
NWMO: non-Western maternal origin
pCMV: postnatal cytomegalovirus
PCR: polymerase chain reaction
RDS: respiratory distress syndrome
SES: socioeconomic status
SGA: small for gestational age
SLS: sepsislike syndrome
SNHL: sensorineural hearing loss
TEA: term-equivalent age
VLBW: very low birth weight
WPPSI-III: Wechsler Preschool and Primary Scale of Intelligence, Third Edition

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