Postnatal Human Cytomegalovirus Infection in Preterm Infants Has Long-Term Neuropsychological Sequelae

Katharina F. Brecht, MSc[1], Rangmar Goelz, MD[2], Andrea Bevot, MD[1], Ingeborg Krägeloh-Mann, MD, PhD[1], Marko Wilke, MD, PhD[1], and Karen Lidzba, PhD[1]

Objective To evaluate whether an early postnatal infection poses a long-term risk for neuropsychological impairment to neonates born very prematurely.

Study design Adolescents born very preterm (n = 42, 11.6-16.2 years, mean = 13.9; 15 girls; 19 with and 23 without an early postnatal human cytomegalovirus [CMV] infection) and typically developing, term born controls (n = 24, 11.3-16.6 years, mean = 13.6; 12 girls) were neuropsychologically assessed with the German version of the Wechsler Intelligence Scale and the Developmental Test for Visual Perception.

Results As expected, the full cohort of adolescents born preterm had significantly lower scores than term born controls on IQ (preterm: mean [SD] = 98.43 [14.83], control: 110.00 [8.10], $P = .015$) and on visuoperceptive abilities (95.64 [12.87] vs 106.24 [9.95], $P = .016$). Furthermore, adolescents born preterm with early postnatal CMV infection scored significantly lower than those without this infection regarding overall cognitive abilities (92.67 [14.71] vs 102.75 [13.67], $P = .030$), but not visuoperceptive abilities (91.22 [10.88] vs 98.96 [13.45], $P > .05$).

Conclusions In our small but well-characterized group, our results provide evidence for adverse effects of early postnatal CMV infection on overall cognitive functions in adolescents born preterm. If confirmed, these results support the implementation of preventive measures. *(J Pediatr 2015;166:834-9)*.

See editorial, p 795 and related article, p 870

With an estimated prevalence of 0.6% in newborn infants, human cytomegalovirus (CMV) is the most common congenital infection worldwide.[1] Such an infection can result in a wide range of brain abnormalities,[2,3] affecting both gray and white matter. A postnatal infection with CMV is defined as an infection (proven by virus detection) within the first year of life but later than 2 weeks after delivery.[4] In term born neonates, a postnatal infection (usually via CMV positive breast milk) is unlikely to cause severe illness because of the placental transmission of protective antibodies after about 28 weeks of gestation.[5] However, the situation is less clear in premature infants.[6]

Because of its nutritional and non-nutritional benefits, human milk is recommended for both preterm and term-born infants.[7] At the same time, human milk is a prominent mode of CMV transmission in early postnatal life of preterm infants[8] because the incidence of CMV reactivation in mothers during lactation is high, particularly following premature birth.[4,9] As evidence for long-term neurobiological consequences of such an infection is inconclusive, prevention strategies are not implemented universally. Although we and others did not find evidence for specific neurologic impairment in the neonatal period and in early childhood,[10-12] our follow-up assessments revealed that cognitive deficits in children born preterm induced by an early postnatal CMV infection do exist and can be detected in later childhood.[13,14] This argues against overt neurologic impairment but suggests possible effect on complex cognitive skills. Because of the direct consequences for handling CMV-positive human milk in the neonatal intensive care unit ("to pasteurize or not to pasteurize"), examining long-term neurobiological consequences is of high relevance. For the present study, we hypothesized that compared with term-born controls (TERM), adolescents born preterm are impaired in general cognitive abilities, as well as in visuoperceptive abilities (independent of general cognitive abilities), and adolescents born preterm with an early postnatal CMV infection (PRE $_{CMV+}$) are similarly, but

CMV	Human cytomegalovirus
DTVP-A	Developmental Test of Visual Perception-Adolescent and Adult
GVPI	General visual perceptual index
HAWIK-IV	Hamburg-Wechsler-Intelligenztest für Kinder IV
MRI	Magnetic resonance imaging
PCR	Polymerase chain reaction
PRE $_{CMV+}$	Adolescents born preterm without postnatal CMV infection
PRE $_{CMV-}$	Adolescents born preterm with postnatal CMV infection
TERM	Term-born controls
VCI	Verbal comprehension index

From the Departments of [1]Pediatric Neurology and Developmental Medicine and [2]Neonatology, University Children's Hospital, Tübingen, Germany

Supported by the Deutsche Forschungsgemeinschaft (WI3630/1-1 and 1-2 [to M.W.]), and a Margarete von Wrangell Scholarship funded by the European Social Fund & Ministry of Science and the Arts, Baden-Württemberg (to K.L.). The authors declare no conflicts of interest.

http://dx.doi.org/10.1016/j.jpeds.2014.11.002

more prominently, affected in both of these domains than adolescents born preterm without early postnatal CMV (PRE $_{CMV-}$).

Methods

The present work is part of an ongoing project investigating the long-term cognitive, motor, and neurobiological outcome of preterm infants with early postnatal CMV infection via breast milk. The entire sample participated in observational studies on neonatal transmission rates,[14,15] and follow-up results of parts of our sample have been previously published, with respect to neurodevelopmental outcome between 2 and 4 years,[10] between 4 and 8 years,[13] and between 6 and 8 years.[14] The current study sample includes children between 11 and 17 years (**Table I**) who underwent neuropsychological, neurologic, and magnetic resonance imaging (MRI) examinations. The study was approved by the ethics committee of the medical faculty of the University of Tübingen.

We included children born very preterm (≤32 weeks of gestation or <1500 g birth weight) treated in the neonatal intensive care unit at University Children's Hospital Tübingen between 1995 and 2000. Maternal CMV serostatus was determined, and breast milk of CMV-IgG-positive mothers as well as urine samples of their breastfed infants were studied biweekly during hospital stay, and in addition, at 3 months of corrected age in the outpatient clinic for postnatal CMV infection indicated by CMV polymerase chain reaction (PCR) and culture positivity. Congenital infection was excluded by a CMV PCR-negative urine sample and ear and throat swabs collected immediately after birth. Virologic laboratory studies have been done at the University Tübingen Institute of Medical Virology and Epidemiology of Viral Diseases, as described previously.[4,11] During the observation period, some infants did not (PRE $_{CMV-}$) and others did develop early postnatal CMV infection proven by CMV PCR-positive and CMV culture-positive urine (PRE $_{CMV+}$). Because only CMV-negative blood products were used in the neonatal intensive care unit, infection via transfusion can be ruled out. For the follow-up study reported here, families of all children participating in the initial cohort (n = 92) were invited via personal mail in spring 2011. Typically, developing children in group TERM between 11 and 17 years were recruited in the summer of 2010 by local press and public announcements. Exclusion criteria for all participants were psychiatric disorders, hearing deficits, and general MRI contraindications (because MRI data were required as part of this project, the results of which are reported elsewhere[15]). For the group TERM, no objective neonatal data was available, nor were they formally screened for CMV infection in the neonatal period. However, neurologic disorders and cognitive impairment as well as any parent-reported signs of infection in the neonatal period (eg, hospital stay or hepatosplenomegaly) were additional exclusion criteria for this group. Written informed consent was obtained from at least 1 parent, and all subjects assented with the procedures. Participants were compensated for time and travel. **Figure 1** (available at www.jpeds.com) illustrates the rates of recruitment and exclusion for the 3 groups. Attrition and exclusion criteria left 42 children in the preterm group (19 PRE $_{CMV+}$/23 PRE $_{CMV-}$) and 24 in group TERM. One participant born preterm (PRE $_{CMV-}$) failed to complete the neuropsychological assessment.

All participants completed the German version of the Wechsler Intelligence Scale for Children-Fourth Edition (Hamburg-Wechsler-Intelligenztest für Kinder IV [HAWIK-IV][16]) to assess general cognitive abilities. In the HAWIK-IV, intelligence is conceived as a global construct, which is comprised of specific factors. The general intellectual level is calculated from 10 subtests, yielding a standardized full-scale IQ as well as 4 subscales representing more specific cognitive abilities (verbal comprehension, perceptual reasoning, processing speed, and working memory indices). The Developmental Test of Visual Perception-Adolescent and Adult (DTVP-A[17]) is constructed to assess visual perceptual and visual-motor abilities, but neither sensation nor cognition.[17] It consists of 6 subscales, yielding a standardized general visual perceptual index (GVPI) as well as indices for visual-motor integration and motor-reduced visual perception. In order to rule out unspecific effects because of attention problems, attention was measured with 2 subtests of the Test of Attentional Performance,[18] namely Alertness (median reaction time in tonic alertness condition) and Visual Scanning (median reaction time in condition with critical

Table I. Demographic data of adolescents who were term-born and preterm-born (grouped according to early postnatal acquisition of CMV)

		Preterm (n = 42)	
	TERM (n = 24)	CMV− (n = 23)	CMV+ (n = 19)
Median age, y (range)*,†	13.9 (11.3-17.8)	15.0 (12.1-16.1)	14.3 (11.5-16.2)
Male sex, %‡	42	71	72
Maternal education, % (L/M/U/H)‡	8/20/25/46	38/33/8/21	28/39/22/11
Median gestational age, wk (range)†	-	28 (23-31)	28 (23-32)
Median birth weight (range)†	-	1015 (650-1560)	1190 (520-1870)
Median percentile birth weight (range)†	-	40 (3-90)	60 (3-97)
Bronchopulmonary dysplasia§ (n)	-	5	1
Retinopathy of prematurity¶ (n)	-	7	8
Intracerebral hemorrhage¶ (n)	-	4	4
Cerebral palsy (n)‡	0	1	0
Overt lesion by MRI (n)*,‡,**	0 (0%)	5 (21%)	4 (21%)

H, higher education; *L*, lower; *M*, middle; *U*, upper.
*TERM vs preterm $P < .05$; all other comparisons not significant.
†Mann-Whitney U-test.
‡χ^2 test.
§Oxygen dependency >36 weeks corrected age.
¶All grades.
**As assessed by pediatric neuroradiologist: all cases are ventricular dilation.