Intelligence and Academic Achievement With Asymptomatic Congenital Cytomegalovirus Infection

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abstract

OBJECTIVES: To examine intelligence, language, and academic achievement through 18 years of age among children with congenital cytomegalovirus infection identified through hospital-based newborn screening who were asymptomatic at birth compared with uninfected infants.

METHODS: We used growth curve modeling to analyze trends in IQ (full-scale, verbal, and nonverbal intelligence), receptive and expressive vocabulary, and academic achievement in math and reading. Separate models were fit for each outcome, modeling the change in overall scores with increasing age for patients with normal hearing (n = 78) or with sensorineural hearing loss (SNHL) diagnosed by 2 years of age (n = 11) and controls (n = 40).

RESULTS: Patients with SNHL had full-scale intelligence and receptive vocabulary scores that were 7.0 and 13.1 points lower, respectively, compared with controls, but no significant differences were noted in these scores among patients with normal hearing and controls. No significant differences were noted in scores for verbal and nonverbal intelligence, expressive vocabulary, and academic achievement in math and reading among patients with normal hearing or with SNHL and controls.

CONCLUSIONS: Infants with asymptomatic congenital cytomegalovirus infection identified through newborn screening with normal hearing by age 2 years do not appear to have differences in IQ, vocabulary or academic achievement scores during childhood, or adolescence compared with uninfected children.

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WHAT'S KNOWN ON THIS SUBJECT: The extent to which children with congenital cytomegalovirus infection who are asymptomatic at birth are at risk for intellectual impairment or low academic achievement throughout childhood is not well established.

WHAT THIS STUDY ADDS: Infants with asymptomatic congenital cytomegalovirus infection identified through newborn screening who have normal hearing by age 2 years do not appear to have differences in IQ, vocabulary or academic achievement scores during childhood, or adolescence compared with uninfected children.

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Approximately 20 000 (0.5%) children are born with congenital cytomegalovirus (CMV) infection annually in the United States,[1,2] of which 85% to 90% appear asymptomatic at birth.[3,4] The extent to which asymptomatic congenital CMV infection is associated with increased risk of intellectual impairment or low academic achievement throughout childhood is not well established. Researchers for several studies have found no differences in intelligence or various cognitive domains among children with asymptomatic congenital CMV infection identified by newborn screening compared with uninfected children.[5–16] The largest study included 159 children with asymptomatic congenital CMV infection and 130 uninfected children between ages 1 to 13 years, although <20% of all children received assessments at age ≥7 years.[5] Most other researchers managed a small number of children with asymptomatic congenital CMV infection (median: 32; range: 15–60)[6–11,16] through ≤5 years of age.[7,9,10,12,13,16] In this study, we examined intelligence, language, and academic achievement among children with asymptomatic congenital CMV infection identified through hospital-based newborn screening and uninfected children managed through age 18 years.

METHODS

Study Population

From 1982 to 1992, newborns delivered at Women's Hospital of Texas (Houston, TX) were screened for congenital CMV infection via urine culture within the first 3 days of life.[17–19] Of 32 543 screened newborns, 135 (0.4%) tested positive for CMV. Ninety-two (68%) infected newborns with no CMV-related signs at birth (ie, purpura and/or petechiae, jaundice, hepatosplenomegaly, microcephaly, elevated liver enzymes, bilirubinemia, hemolytic anemia, or thrombocytopenia) were enrolled in a longitudinal study as asymptomatic patients along with 42 unmatched controls identified among 298 infants who tested negative for CMV and were born within 6 days of a birth of an infant who tested positive for CMV.[19] All children received audiological assessments from birth to age 18 years. Sensorineural hearing loss (SNHL) outcomes have been previously described for this cohort,[19] as well as IQ at age ≥6 years for a subgroup of 58 patients and 12 children with symptomatic congenital CMV disease.[20] For this analysis, we categorized children on the basis of their hearing status by age 2 years. Children diagnosed with SNHL (ie, ≥25 dB hearing level at any frequency) after age 2 years were categorized as having normal hearing; none of the controls were diagnosed with SNHL by age 2 years. Thus, our analysis included patients with normal hearing, patients with SNHL, and controls.

Neurodevelopmental Assessments

Neurodevelopmental pediatricians and/or psychologists assessed study children by using norm-referenced instruments appropriate for age and verbal ability, ensuring proper accommodations for those with SNHL or whose first language was not English were provided during testing (eg, children used their hearing aids and/or were accompanied by a sign or foreign language interpreter). Assessments were conducted at least once during the infancy, preschool, elementary school, middle school, and high school years, including measures of intelligence, language skills, and academic achievement.

We analyzed longitudinal trends in IQ (full-scale, verbal, and nonverbal intelligence) combining scores from the Wechsler Intelligence Scale for Children (WISC), third edition,[21] and the Wechsler Abbreviated Scale of Intelligence (WASI)[22] at ages 6 to 18 years; the WISC was subsequently replaced by the WASI in later years of the study. We also analyzed trends by combining full-scale intelligence scores from the WISC and WASI[21,22] with the mental scale score from the Bayley Scales of Infant Development[23] at ages 0 to 1 year and the general cognitive index score from the McCarthy Scales of Children's Abilities[24] at ages 2 to 5 years. Because trends for the full-scale intelligence with and without tests at younger ages were similar, we report results of the analysis including scores from all tests.

For language skills, we assessed receptive vocabulary (the ability to understand words) by using the Peabody Picture Vocabulary Test, Revised[25] and expressive vocabulary (the ability to communicate using words) by using the Expressive One Word Picture Test, Revised.[26] For academic achievement, we assessed the broad math and broad reading scores of the Woodcock-Johnson Tests of Achievement, Revised.[27] Scores on all tests have a mean of 100 with an SD of 15 or 16. We categorized children with any of the intelligence scores <85 as at risk for intellectual impairment[28] and those with academic achievement scores in math or reading <85 as having low academic achievement.

Statistical Analysis

We compared maternal sociodemographic characteristics collected at birth, including age, race and/or ethnicity, marital status, education, health insurance, and socioeconomic status between patients with normal hearing, patients with SNHL, and controls by using Fisher's exact test. Socioeconomic status was derived by combining census data on socioeconomic characteristics by zip code of residence at birth and health insurance information.[29] We used growth curve modeling[30] to

analyze trends in full-scale, verbal, and nonverbal intelligence, receptive and expressive vocabulary, and academic achievement in math and reading with increasing age. For each neurodevelopmental measure, we initially fit a model including the child's age, group (ie, patient with normal hearing, patient with SNHL, or control), and mother's education (some college or less versus graduated college or more) because of its potential impact on children's outcomes. The initial models included a small number of variables; thus, we did not adjust for multiple comparisons. We modeled the change in overall scores with age linearly unless there was curvature in the scores with age, in which case we added a quadratic term for age. We included random effects for intercepts and slopes. We used the likelihood ratio test and backward elimination to remove the least significant variable one by one until all variables in the model remained significant at $P < .05$. We report the effect estimate and SE for each variable that was significant in the final models. We calculated the mean test scores for each group of children adjusting for maternal education if it was significant in the final model. We report mean scores and likelihood 95% confidence intervals (CIs) at ages 5 and 18 years for scores that increased linearly with age and at ages 5, 12, and 18 years for scores that showed a curvature with age. We performed data analysis by using SAS (version 9.3; SAS Institute, Cary, NC) and R software (version 3.2.1; R Foundation for Statistical Computing, Vienna, Austria) and fitted growth curve models by using the R package "lme4."[31]

RESULTS

Eighty-nine (97%) of 92 patients and 40 (95%) of 42 controls enrolled in the longitudinal study had neurodevelopmental assessments and were included in this analysis. Overall, 20 patients and 3 controls were diagnosed with SNHL at median ages of 16 months (range: 1 month–18 years) and 11 years (range: 9–15), respectively. Eleven patients were diagnosed with SNHL by age 2 years, among whom 9 had moderate to profound SNHL (>40 dB) at age 2 years; 2 progressed to those levels later. All 9 patients and 3 controls diagnosed with SNHL after age 2 years had SNHL ≤40 dB in the poorer-hearing ear except 1 patient diagnosed with mild unilateral SNHL at age 5 years, which progressed to severe by age 8 years. Thus, our analyses consisted of comparisons among 78 patients with normal hearing, 11 patients with SNHL by age 2 years, and 40 controls.

TABLE 1 Demographic Characteristics of Patients With and Without SNHL by Age 2 y and Controls

Demographic Characteristics	Patients With Normal Hearing ($N = 78$), *n* (%)	Patients With SNHL ($N = 11$), *n* (%)	Controls ($N = 40$), *n* (%)	*P*
Sex				.14
Boy	43 (55)	8 (73)	29 (73)	
Girl	35 (45)	3 (27)	11 (28)	
Mother's age				.88
<20 y	1 (1)	0 (0)	0 (0)	
20–29 y	48 (62)	7 (64)	22 (55)	
30–39 y	28 (36)	4 (36)	18 (45)	
40–49 y	1 (1)	0 (0)	0 (0)	
Mother's race and/or ethnicity				.68
Non-Hispanic white	64 (82)	11 (100)	35 (88)	
Non-Hispanic African American	8 (10)	0 (0)	4 (10)	
Hispanic	6 (8)	0 (0)	1 (3)	
Mother's marital status				.65
Single	4 (5)	0 (0)	0 (0)	
Married	70 (90)	10 (91)	37 (93)	
Divorced	3 (4)	1 (9)	2 (5)	
Separated	1 (1)	0 (0)	1 (3)	
Mother's education				.37
Up to high school graduate	21 (27)	1 (9)	6 (15)	
Some college	24 (31)	6 (55)	13 (33)	
Graduated college	25 (32)	2 (18)	17 (43)	
Postgraduate degree	8 (10)	2 (18)	4 (10)	
Health insurance				<.01
None	3 (4)	0 (0)	1 (2)	
Private and/or HMO	60 (77)	7 (64)	19 (48)	
Medicaid	0 (0)	1 (9)	0 (0)	
Other or unknown	15 (19)	3 (27)	20 (50)	
Socioeconomic status				.35
Low	3 (4)	1 (9)	1 (2)	
Medium	28 (36)	4 (36)	9 (23)	
High	47 (60)	6 (55)	30 (75)	

HMO, health maintenance organization.

A majority of the children were born to non-Hispanic white mothers, aged 20 to 40 years, married, who had at least some college education and medium or high socioeconomic status, with no statistically significant differences among the 3 groups except for health insurance status (Table 1). The median age at last assessment among all 3 groups was 13 years for expressive vocabulary and 17 years for all other measures (Table 2). The median number of measures of full-scale intelligence (including tests at younger ages) was greater among patients with normal hearing or with SNHL compared with controls.

Intelligence

Among 75 patients with normal hearing, 11 patients with SNHL,

TABLE 2 Neurodevelopmental Assessments Among Patients With Normal Hearing or With SNHL by Age 2 y and Controls

Neurodevelopmental Assessment	Patients With Normal Hearing (*N* = 78)	Patients With SNHL (*N* = 11)	Controls (*N* = 40)
Full-scale intelligence			
No. of children tested (%)	75 (96)	11 (100)	39 (98)
Median no. of tests (IQR)	7 (5–8)	7 (6–8)	4 (2–5)
Median age at last assessment, y (IQR)	17.1 (14.5–17.5)	17.7 (17.4–18.3)	17.1 (14.6–17.6)
Verbal intelligence			
No. of children tested (%)	72 (92)	10 (91)	35 (88)
Median no. of tests (IQR)	4 (3–4)	4 (4–4)	3 (2–4)
Median age at last assessment, y (IQR)	17.2 (15.8–17.6)	17.8 (17.5–17.9)	17.4 (16.6–17.7)
Nonverbal intelligence			
No. of children tested (%)	72 (92)	11 (100)	35 (88)
Median no. of tests (IQR)	4 (3–4)	4 (3–4)	3 (2–4)
Median age at last assessment, y (IQR)	17.2 (15.8–17.6)	17.7 (17.4–17.9)	17.4 (16.6–17.7)
Receptive vocabulary			
No. of children tested (%)	72 (92)	11 (100)	35 (88)
Median no. of tests (IQR)	3 (2–4)	4 (3–5)	2 (2–3)
Median age at last assessment, y (IQR)	17.1 (14.6–17.6)	17.7 (17.4–17.9)	17.2 (15.6–17.6)
Expressive vocabulary			
No. of children tested (%)	70 (90)	11 (100)	33 (83)
Median no. of tests (IQR)	2.5 (2–3)	3 (2–3)	1 (1–2)
Median age at last assessment, y (IQR)	13.3 (10.1–13.7)	13.2 (11.3–13.6)	13.4 (12.3–14.1)
Academic achievement: math			
No. of children tested (%)	70 (90)	11 (100)	35 (88)
Median no. of tests (IQR)	3 (2–4)	3 (3–4)	2 (2–3)
Median age at last assessment, y (IQR)	17.2 (16.4–17.6)	17.7 (17.4–17.9)	17.4 (16.9–17.7)
Academic achievement: reading			
No. of children tested (%)	70 (90)	11 (100)	35 (88)
Median no. of tests (IQR)	3 (2–4)	3 (3–4)	2 (2–3)
Median age at last assessment, y (IQR)	17.2 (16.4–17.6)	17.7 (17.4–17.9)	17.2 (16.4–17.6)

IQR, interquartile range.

and 39 controls, scores <85 were recorded as follows: 6 (8%), 3 (27%), and 5 (13%), respectively, on the Bayley scales; 6 (8%), 2 (18%), 3 (8%) on the McCarthy scales; and 4 (5%), 1 (9%), and 3 (8%) on the WISC and/or WASI. Among children with scores <85 on the Bayley scales, 4 patients with normal hearing and 1 patient with SNHL were lost to follow-up; only 1 patient with normal hearing and 1 control had scores <85 in more than 1 assessment.

Full-scale intelligence scores increased linearly with increasing age (0.2 points per year, SE = 0.1; $P < .05$), but the rate of change did not differ among the 3 groups. Mean (95% CI) full-scale intelligence scores adjusted for mother's education at age 5 and 18 years were, respectively, 108 (105–110) and 111 (108–114) for patients with normal hearing, 101 (95–106) and 104 (98–110) for patients with SNHL, and 108 (104–111) and 111 (107–114) for controls. Full-scale intelligence scores for patients with normal hearing did not differ from controls at either time point ($P = .96$). Patients with SNHL had scores that were 7.0 (SE = 0.3) points lower compared with controls ($P < .05$). Children of mothers who graduated college had full-scale intelligence scores that were 3.5 (SE = 1.7) points higher compared with children of mothers with some college or less education ($P < .05$).

Verbal and nonverbal intelligence scores did not change significantly with increasing age. Mean (95% CI) verbal and nonverbal intelligence scores adjusted for mother's education were 107 (105–109) and 109 (107–111), respectively, with no significant differences among the 3 groups. Children of mothers who graduated college had verbal and nonverbal scores that were 4.4 (SE = 2.1) and 4.0 (SE = 1.9) points higher, respectively, compared with children of mothers with some college or less education ($P < .05$ for both).

Language

Receptive vocabulary scores increased until 12.5 years and declined slightly thereafter (effect estimates [SD]: 3.0 [0.5] for linear term and 0.1 [0.02] for quadratic term; $P < .001$ for both). Mean (95% CI) receptive vocabulary scores at ages 5, 12, and 18 years were 100 (97–103), 107 (104–110), and 104 (100–107) for patients with normal hearing, respectively; 89 (82–97), 96 (89–104), and 93 (85–101) for patients with SNHL; and 102 (98–107), 109 (105–114), and 106 (101–111) for controls. Patients with SNHL had receptive vocabulary scores that were 13.1 (SE = 4.2) points lower compared with controls ($P < .05$); the difference in scores between patients with normal hearing and controls was not statistically significant (2.4; SE = 2.6; $P = .36$).

Expressive vocabulary scores decreased linearly with increasing age for all 3 groups (1.8 points per year; SE = 0.3; $P < .05$). Mean (95% CI) expressive vocabulary scores at ages 5 and 18 years were 120 (115–125) and 96 (91–101), with no significant differences among the 3 groups. Maternal education was not significantly associated with either receptive or expressive language scores for any of the groups. The pattern of change in either receptive

or expressive vocabulary scores did not differ among the 3 groups.

Academic Achievement

Among 70 patients with normal hearing, 8 (11%) had low academic achievement (scores <85; 6 in math only, 1 in reading, 1 in both). None of the 11 patients with SNHL had low academic achievement in math or reading. One (3%) of 39 controls had low academic achievement in math.

Academic achievement scores in math decreased linearly with increasing age for all 3 groups (0.6 points per year; SE = 0.2; $P < .05$). Mean (95% CI) math scores adjusted for mother's education were 117 (113–121) at age 5 years and 109 (106–112) at age 18 years, with no significant differences among the 3 groups. Children of mothers who graduated college had scores that were 7.4 (SE = 2.6) points higher compared with children of mothers with some college or less education ($P < .05$).

Academic achievement scores in reading did not change with increasing age. The mean (95% CI) reading score adjusted for mother's education was 112 (109–114), with no significant differences among the 3 groups. Children of mothers who graduated college had scores that were 6.5 (SE = 2.5) points higher compared with children of mothers with some college or less education ($P < .05$).

DISCUSSION

In this study, infants with congenital CMV infection who were asymptomatic at birth with normal hearing by age 2 years were not at increased risk for intellectual impairment or low academic achievement compared with uninfected controls throughout adolescence. This confirms findings of smaller studies that revealed no significant difference in intelligence measures through early or late childhood.[6,7,9–11,13,14,32] Our study included infants identified through hospital-based newborn screening managed through adolescence and provides new information on intellectual functioning, language, and academic achievement of children with asymptomatic congenital CMV infection with and without SNHL compared with a group of uninfected children.

Approximately 85% to 90% of children with congenital CMV infection are asymptomatic at birth. Findings from our study suggest that the majority of children that would be identified by newborn screening do not appear to be at increased risk of intellectual impairment and, therefore, may not need long-term monitoring for cognitive impairment and/or disabilities. Although this information could provide reassurance to parents, the psychosocial consequences (including increased parental anxiety) and other family-level impacts of CMV screening (ie, time and costs incurred for regular monitoring) need to be systematically evaluated.[33] More research is needed to understand the cost-benefit and minimize potential adverse psychosocial consequences of newborn screening for congenital CMV infection.

Although we found no increased risk of intellectual impairment in children with asymptomatic congenital CMV infection, we did observe that children who had asymptomatic congenital CMV infection and developed SNHL by age 2 years had full-scale intelligence and receptive vocabulary scores that were lower than controls. However, their nonverbal intelligence and academic achievement scores in math and reading were not significantly different from controls, suggesting that the full-scale intelligence scores in patients with SNHL were an underestimate of their intellectual potential. We are not aware of any study whose researchers have assessed the impact of SNHL on intelligence among children with asymptomatic congenital CMV infection. Significant differences in receptive vocabulary scores between patients and controls were likely attributable to SNHL rather than asymptomatic congenital CMV infection. Previously, we reported that the prevalence of SNHL among our asymptomatic patients nearly doubled from ages 3 to 24 months.[19] Data from the CMV and Hearing Multicenter Screening Study revealed that nearly half of children with asymptomatic congenital CMV infection who are diagnosed with SNHL within 8 weeks of age are missed by newborn hearing screening.[34] Screening of newborns for congenital CMV infection may allow early identification of SNHL in children with asymptomatic congenital CMV infection[34] so that they can receive appropriate interventions to minimize delays in their communication, cognition, reading, and social-emotional development.[35] However, there is currently no consensus on audiologic monitoring for children with asymptomatic congenital CMV infection.[36]

In our cohort, we observed trends in intelligence, language, and academic achievement that were intriguing. We found a modest increase in full-scale intelligence scores with increasing age in patients with either normal hearing or SNHL and in controls. Trends and mean scores were similar when restricting the analysis to the WISC and WASI, which are administered to children between 6 and 18 years of age and provide more comparable measures of intelligence. Because intelligence measures are expected to remain unchanged over time, it is possible that the increasing scores with age reflect literacy or cultural gains among children, a phenomenon described as the Flynn effect.[37] Previous studies of children

with asymptomatic congenital CMV infection have also revealed slightly higher scores at older ages although the groups under comparison did not necessarily include the same group of children managed over time.[5,6] In contrast to the increasing trend in intelligence scores with increasing age, we found that receptive vocabulary scores increased up to age 12.5 years and then decreased, whereas scores for expressive vocabulary decreased with increasing age. These trends in receptive and expressive vocabulary scores were similar when excluding children who developed SNHL after age 2 years. Furthermore, scores in academic achievement in math, but not in reading, appeared to decrease with increasing age in all 3 groups. It is unclear if the amount of change in test scores that would be explained by age is of clinical importance. Nonetheless, it is possible that other domains of intellectual functioning (eg, attention) or other factors (eg, social or environmental) could have influenced children's expressive vocabulary and academic achievement in math.

Our study had several strengths. Newborns with asymptomatic congenital CMV infection were identified through hospital-based screening, providing an opportunity to assess the full spectrum of outcomes among these children. The uninfected newborns managed as controls had no significant differences in sociodemographic characteristics. Thus, the control group appeared to have been valid for comparisons. The comprehensive neurodevelopmental follow-up with multiple assessments through adolescence was important for understanding variability in scores over time. Finally, the robust analytical approach allowed for examination of trends in scores while controlling for variability within and between groups and imbalances in the number of assessments.

Nonetheless, our study had some limitations. Not all infants with congenital CMV infection identified through newborn screening were enrolled in the study, and the number of uninfected children enrolled as controls was relatively small. A majority of children were born to mothers with at least some college education and medium or high socioeconomic status. Thus, the findings may not be generalized to populations with lower education level and/or socioeconomic status.[38] Our sample size was not large enough to include other potential risk factors in the analysis. Our control group had fewer evaluations than our patients. Nevertheless, the median age at the last assessment among the 3 groups was similar. We did not assess whether there were differences in specific cognitive domains, such as attention, perception, memory, and executive functioning, although we found no significant differences between patients and controls in exploratory analysis (not shown). Finally, data on interventions provided to children identified with asymptomatic infection were not systematically collected or assessed. Interventions provided for patients with SNHL may have helped minimize the impact of hearing loss on their intellectual functioning.

CONCLUSIONS

Our study suggests that infants with asymptomatic congenital CMV infection identified through newborn screening with normal hearing by age 2 years do not appear to have differences in IQ, vocabulary, or academic achievement scores during childhood or adolescence compared with uninfected children. The implication that children with asymptomatic congenital CMV infection at birth may not need long-term monitoring for cognitive impairment and/or disabilities based on current evidence is of clinical importance. Further studies are needed to better understand the impact of asymptomatic congenital CMV infection on behavior and specific cognitive domains such as attention, perception, and memory.

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ABBREVIATIONS

CI: confidence interval
CMV: cytomegalovirus
SNHL: sensorineural hearing loss
WASI: Wechsler Abbreviated Scale of Intelligence
WISC: Wechsler Intelligence Scale for Children

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REFERENCES

1. Boppana SB, Ross SA, Novak Z, et al; National Institute on Deafness and Other Communication Disorders CMV and Hearing Multicenter Screening (CHIMES) Study. Dried blood spot real-time polymerase chain reaction assays to screen newborns for congenital cytomegalovirus infection. *JAMA*. 2010;303(14):1375–1382
2. Boppana SB, Ross SA, Shimamura M, et al; National Institute on Deafness and Other Communication Disorders CHIMES Study. Saliva polymerase-chain-reaction assay for cytomegalovirus screening in newborns. *N Engl J Med*. 2011;364(22):2111–2118
3. Cannon MJ, Griffiths PD, Aston V, Rawlinson WD. Universal newborn screening for congenital CMV infection: what is the evidence of potential benefit? *Rev Med Virol*. 2014;24(5):291–307
4. Dollard SC, Grosse SD, Ross DS. New estimates of the prevalence of neurological and sensory sequelae and mortality associated with congenital cytomegalovirus infection. *Rev Med Virol*. 2007;17(5):355–363
5. Kashden J, Frison S, Fowler K, Pass RF, Boll TJ. Intellectual assessment of children with asymptomatic congenital cytomegalovirus infection. *J Dev Behav Pediatr*. 1998;19(4):254–259
6. Temple RO, Pass RF, Boll TJ. Neuropsychological functioning in patients with asymptomatic congenital cytomegalovirus infection. *J Dev Behav Pediatr*. 2000;21(6):417–422
7. Kumar ML, Nankervis GA, Gold E. Inapparent congenital cytomegalovirus infection. A follow-up study. *N Engl J Med*. 1973;288(26):1370–1372
8. Kumar ML, Gold E, Jacobs IB, Ernhart CB, Nankervis GA. Primary cytomegalovirus infection in adolescent pregnancy. *Pediatrics*. 1984;74(4):493–500
9. Williamson WD, Percy AK, Yow MD, et al. Asymptomatic congenital cytomegalovirus infection. Audiologic, neuroradiologic, and neurodevelopmental abnormalities during the first year. *Am J Dis Child*. 1990;144(12):1365–1368
10. Reynolds DW, Stagno S, Stubbs KG, et al. Inapparent congenital cytomegalovirus infection with elevated cord IgM levels. Casual relation with auditory and mental deficiency. *N Engl J Med*. 1974;290(6):291–296
11. Conboy TJ, Pass RF, Stagno S, et al. Intellectual development in school-aged children with asymptomatic congenital cytomegalovirus infection. *Pediatrics*. 1986;77(6):801–806
12. Saigal S, Lunyk O, Larke RP, Chernesky MA. The outcome in children with congenital cytomegalovirus infection. A longitudinal follow-up study. *Am J Dis Child*. 1982;136(10):896–901
13. Pearl KN, Preece PM, Ades A, Peckham CS. Neurodevelopmental assessment after congenital cytomegalovirus infection. *Arch Dis Child*. 1986;61(4):323–326
14. Ivarsson SA, Lernmark B, Svanberg L. Ten-year clinical, developmental, and intellectual follow-up of children with congenital cytomegalovirus infection without neurologic symptoms at one year of age. *Pediatrics*. 1997;99(6):800–803
15. Townsend CL, Forsgren M, Ahlfors K, Ivarsson SA, Tookey PA, Peckham CS. Long-term outcomes of congenital cytomegalovirus infection in Sweden and the United Kingdom. *Clin Infect Dis*. 2013;56(9):1232–1239
16. Shan R, Wang X, Fu P. Growth and development of infants with asymptomatic congenital cytomegalovirus infection. *Yonsei Med J*. 2009;50(5):667–671
17. Yow MD, Williamson DW, Leeds LJ, et al. Epidemiologic characteristics of

cytomegalovirus infection in mothers and their infants. *Am J Obstet Gynecol*. 1988;158(5):1189–1195

18. Williamson WD, Demmler GJ, Percy AK, Catlin FI. Progressive hearing loss in infants with asymptomatic congenital cytomegalovirus infection. *Pediatrics*. 1992;90(6):862–866
19. Lanzieri TM, Chung W, Flores M, et al; Congenital Cytomegalovirus Longitudinal Study Group. Hearing loss in children with asymptomatic congenital cytomegalovirus infection. *Pediatrics*. 2017;139(3):e20162610
20. Noyola DE, Demmler GJ, Williamson WD, et al; Congenital CMV Longitudinal Study Group. Cytomegalovirus urinary excretion and long term outcome in children with congenital cytomegalovirus infection. *Pediatr Infect Dis J*. 2000;19(6):505–510
21. Wechsler D. *Wechsler Intelligence Scale for Children*. 3rd ed. San Antonio, TX: The Psychological Corporation; 1991
22. Wechsler D. *Wechsler Abbreviated Scale of Intelligence*. San Antonio, TX: The Psychological Corporation; 1999
23. Bayley N. *Bayley Scales of Infant Development*. San Antonio, TX: Psychological Corporation; 1969
24. McCarthy D. *McCarthy Scale of Children's Abilities*. New York, NY: Psychological Corp; 1972
25. Dunn LM, Dunn LM. *Examiner's Manual for the Peabody Picture Vocabulary Test, Revised Edition*. Circle Pines, MN: American Guidance Service; 1981
26. Gardner MF. *The Expressive One Word Picture Vocabulary Test, Revised*. Novato, CA: Academic Therapy Publications; 1983
27. Woodcock RW, Johnson MB. *Manual for the Woodcock-Johnson Tests of Achievement- Revised*. Allen, TX: RCL Enterprises; 1990
28. Sampath V, Bowen J, Gibson F. Risk factors for adverse neurodevelopment in extremely low birth weight infants with normal neonatal cranial ultrasound. *J Perinatol*. 2005;25(3):210–215
29. Singh GK, Miller BA, Hankey BF, Edwards BK. Persistent area socioeconomic disparities in U.S. incidence of cervical cancer, mortality, stage, and survival, 1975-2000. *Cancer*. 2004;101(5):1051–1057
30. Raudenbush SW, Bryk AS. *Hierarchical Linear Models: Applications and Data Analysis Methods*. 2nd ed. Thousand Oaks, CA: SAGE Publications; 2002
31. Bates D, Maechler M, Bolker BM, Walker S. Fitting linear mixed-effects models using lme4.*J Stat Softw*. 2015;67(1):1–48
32. Kumar ML, Nankervis GA, Jacobs IB, et al. Congenital and postnatally acquired cytomegalovirus infections: long-term follow-up. *J Pediatr*. 1984;104(5):674–679
33. Grosse SD, Dollard S, Ross DS, Cannon M. Newborn screening for congenital cytomegalovirus: options for hospital-based and public health programs. *J Clin Virol*. 2009;46(suppl 4):S32–S36
34. Fowler KB, McCollister FP, Sabo DL, et al; CHIMES Study. A targeted approach for congenital cytomegalovirus screening within newborn hearing screening. *Pediatrics*. 2017;139(2):e20162128
35. American Academy of Pediatrics, Joint Committee on Infant Hearing. Year 2007 position statement: principles and guidelines for early hearing detection and intervention programs. *Pediatrics*. 2007;120(4):898–921
36. Grosse SD, Dollard SC, Kimberlin DW. Screening for congenital cytomegalovirus after newborn hearing screening: what comes next? *Pediatrics*. 2017;139(2):e20163837
37. Shenk D. What is the Flynn effect, and how does it change our understanding of IQ? *Wiley Interdiscip Rev Cogn Sci*. 2017;8(1–2):e1366
38. Breslau N, Chilcoat HD, Susser ES, Matte T, Liang KY, Peterson EL. Stability and change in children's intelligence quotient scores: a comparison of two socioeconomically disparate communities. *Am J Epidemiol*. 2001;154(8):711–717

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