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Intelligence and academic achievement with asymptomatic congenital cytomegalovirus infection

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Abstract

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Contributor's Statement:
Adriana S. Lopez conceptualized and conducted analysis contained in this report, interpreted the data, led the writing of the initial manuscript, revised the manuscript and approved the final version.
Tatiana M. Lanzieri conceptualized and conducted analysis contained in this report, interpreted the data, revised the manuscript and approved the final version.
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Jerry A. Miller assisted with data management and quality control for the Longitudinal Congenital CMV Study, revised the manuscript and approved the final version.
Craig M. Hales conducted analysis contained in this report, interpreted the data, revised the manuscript and approved the final version.
Stephanie R. Bialek conceptualized the analysis contained in this report, interpreted the data, revised the manuscript and approved the final version.
Gail Demmler-Harrison was the Principal Investigator for the Longitudinal Congenital CMV Study, provided patient follow-up, revised the manuscript and approved the final version.

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

Methods—We used growth curve modeling to analyze trends in intelligence quotient (full-scale, verbal and non-verbal 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 case-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—Case-patients with SNHL had full-scale intelligence and receptive vocabulary scores that were 7.0 and 13.1 points lower, respectively, compared to controls, but no significant differences were noted in these scores among case-patients with normal hearing and controls. No significant differences were noted in scores for verbal and non-verbal intelligence, expressive vocabulary, and academic achievement in math and reading among case-patients with normal hearing or with SNHL and controls.

Conclusions—Infants with asymptomatic congenital CMV infection identified through newborn screening with normal hearing by age 2 years do not appear to have differences in intelligence quotient, vocabulary or academic achievement scores during childhood or adolescence compared with uninfected children.

TOC image

Intelligence, language and academic achievement in children with asymptomatic congenital CMV infection identified through hospital-based newborn screening followed through 18 years of age

Keywords

congenital cytomegalovirus; intelligence; language; academic achievement; sensorineural hearing loss

INTRODUCTION

Approximately 20,000 (0.5%) children are born with congenital cytomegalovirus (CMV) infection annually in the United States[1, 2], of which 85–90% 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. Several studies have found no differences in intelligence or various cognitive domains among children with asymptomatic congenital CMV infection identified by newborn screening compared to uninfected children.[5–16] The largest study included 159 children with asymptomatic congenital CMV infection and 130 uninfected children between ages 1–13 years, although <20% of all children received assessments at age ≥7 years.[5] Most other studies followed 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 followed through age 18 years.

METHODS

Study population

During 1982–1992, 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%) were CMV-positive. Ninety-two (68%) infected newborns with no CMV-related signs at birth (i.e. purpura/petechiae, jaundice, hepatosplenomegaly, microcephaly, elevated liver enzymes, bilirubinemia, hemolytic anemia or thrombocytopenia) were enrolled in a longitudinal study as asymptomatic case-patients, along with 42 unmatched controls identified among 298 CMV-negative infants born within 6 days of a CMV-positive infant's birth.[19] All children received audiological assessments from birth to age 18 years. SNHL outcomes have been previously described for this cohort[19], as well as intelligence quotient at age ≥6 years for a subgroup of 58 case-patients and 12 children with symptomatic congenital CMV disease.[20] For this analysis, we categorized children based on their hearing status by age 2 years. Children diagnosed with SNHL (i.e. ≥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 case-patients with normal hearing, case-patients with SNHL, and controls.

Neurodevelopmental assessments

Neurodevelopmental pediatricians and/or psychologists assessed study children using norm-referenced instruments appropriate for age and verbal ability, ensuring proper accomodations for those with SNHL or whose first language was not English were provided during testing, e.g. 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, pre-school, elementary, middle, and high school years, including measures of intelligence, language skills, and academic achievement.

We analyzed longitudinal trends in intelligence quotient (full-scale, verbal and non-verbal intelligence) combining scores from the Wechsler Intelligence Scale for Children (WISC) 3rd edition[21] and the Wechsler Abbreviated Scale of Intelligence (WASI)[22] at ages 6–18 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 0–1 year and the general cognitive index score from the McCarthy Scales of Children's Abilities[24] at ages 2–5 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, using the Peabody Picture Vocabulary Test – Revised[25], and expressive vocabulary, the ability to communicate using words, 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 a standard deviation 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/ethnicity, marital status, education, health insurance, and socioeconomic status between case-patients with normal hearing, with SNHL and controls 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 non-verbal 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 (i.e., case-patient with normal hearing, case-patient with SNHL, or control), and mother's education (some college or less vs. 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 $P<0.05$. We report the effect estimate and standard error (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 (CI) 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 using SAS (version 9.3, SAS Institute, Cary, North Carolina) and R software (version 3.2.1, R Foundation for Statistical Computing, Vienna, Austria), and fitted growth curve models using the R package "lme4."[31]

RESULTS

Eighty-nine (97%) of 92 case-patients and 40 (95%) of 42 controls enrolled in the longitudinal study had neurodevelopmental assessments and were included in this analysis. Overall, 20 case-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 case-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 case-patients and 3 controls diagnosed with SNHL after age 2 years had SNHL ≤40 dB in the poorer-hearing ear, except one case-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 case-patients with normal hearing, 11 case-patients with SNHL by age 2 years, and 40 controls.

A majority of the children were born to non-Hispanic white mothers, aged 20–40 years, married, who had at least some college education and medium/high socioeconomic status,

with no statistically significant differences among the 3 groups, except for health insurance status (Table 1). Median age at last assessment among all 3 groups was 13 years for expressive vocabulary and 17 years for all other measures (Table 2). Median number of measures of full-scale intelligence (including tests at younger ages) was greater among case-patients with normal hearing or with SNHL compared with controls.

Intelligence

Among 75 case-patients with normal hearing, 11 case-patients with SNHL, 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 in the Bayley scales, 4 case-patients with normal hearing and 1 case-patient with SNHL were lost to follow-up; only 1 case-patient with normal hearing and one control had scores <85 in more than one assessment.

Full-scale intelligence scores increased linearly with increasing age (0.2 points per year, SE=0.1; P<0.05), 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 case-patients with normal hearing, 101 (95–106) and 104 (98–110) for case-patients with SNHL, and 108 (104–111) and 111 (107–114) for controls. Full-scale intelligence scores for case-patients with normal hearing did not differ from controls at either time point (P=0.96). Case-patients with SNHL had scores that were 7.0 (SE=0.3) points lower compared to controls (P<0.05). Children of mothers who graduated college had full-scale intelligence scores that were 3.5 (SE=1.7) points higher compared to children of mothers with some college or less education (P<0.05).

Verbal and non-verbal intelligence scores did not change significantly with increasing age. Mean (95% CI) verbal and non-verbal 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 non-verbal scores that were 4.4 (SE=2.1) and 4.0 (SE=1.9) points higher, respectively, compared to children of mothers with some college or less education (P<0.05 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<0.001 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 case-patients with normal hearing, respectively; 89 (82–97), 96 (89–104), and 93 (85–101) for case-patients with SNHL; and 102 (98–107), 109 (105–114), and 106 (101–111) for controls. Case-patients with SNHL had receptive vocabulary scores that were 13.1 (SE=4.2) points lower compared to controls (P<0.05); the difference in scores between case-patients with normal hearing and controls was not statistically significant (2.4; SE=2.6; P=0.36).

Expressive vocabulary scores decreased linearly with increasing age for all 3 groups (1.8 points per year; SE=0.3; P<0.05). 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 case-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 case-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<0.05). 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 to children of mothers with some college or less education (P<0.05).

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 to children of mothers with some college or less education (P<0.05).

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 to uninfected controls throughout adolescence. This confirms findings of smaller studies which found 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 followed 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 to a group of uninfected children.

About 85–90% 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/disabilities. Although this information could provide reassurance to parents, the psychosocial consequences, including increased parental anxiety, and other family-level impacts of CMV screening (i.e. 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 non-verbal intelligence and academic achievement scores in math and reading were not significantly different than controls, suggesting that the full-scale intelligence scores in case-patients with SNHL were an underestimate of their intellectual potential. We are not aware of any study that has assessed the impact of SNHL on intelligence among children with asymptomatic congenital CMV infection. Significant differences in receptive vocabulary scores between case-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 case-patients nearly doubled from ages 3 months 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 case-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 6–18 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 found slightly higher scores at older ages though the groups under comparison did not necessarily include the same group of children followed 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, while 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 (e.g. attention) or other factors (e.g., social, 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 followed 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/high socioeconomic status. Thus, the findings may not be generalized to populations with lower education level/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 case-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, though we found no significant differences between case-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 case-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 intelligence quotient, 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/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

CMV	cytomegalovirus
SNHL	sensorineural hearing loss

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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 CMV infection identified through newborn screening who have normal hearing by age 2 years do not appear to have differences in intelligence quotient, vocabulary or academic achievement scores during childhood or adolescence compared with uninfected children.

Table 1

Demographic characteristics of case-patients with and without sensorineural hearing loss by age 2 years and controls

Demographic characteristics	Case-patients with normal hearing (n=78) n (%)	Case-patients with SNHL (n=11) n (%)	Controls (n=40) n (%)	P-value
Gender				
Male	43 (55)	8 (73)	29 (73)	0.14
Female	35 (45)	3 (27)	11 (28)	
Mother' age				
<20 years	1 (1)	0 (0)	0 (0)	
20–29 years	48 (62)	7 (64)	22 (55)	0.88
30–39 years	28 (36)	4 (36)	18 (45)	
40–49 years	1 (1)	0 (0)	0 (0)	
Mother' race/ethnicity				
Non-Hispanic White	64 (82)	11 (100)	35 (88)	
Non-Hispanic Black	8 (10)	0 (0)	4 (10)	0.68
Hispanic	6 (8)	0 (0)	1 (3)	
Mother' marital status				
Single	4 (5)	0 (0)	0 (0)	
Married	70 (90)	10 (91)	37 (93)	0.65
Divorced	3 (4)	1 (9)	2 (5)	
Separated	1 (1)	0 (0)	1 (3)	
Mother' education				0.37
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)	
Post-graduate degree	8 (10)	2 (18)	4 (10)	
Health insurance				
None	3 (4)	0 (0)	1 (2)	
Private/HMO	60 (77)	7 (64)	19 (48)	<0.01
Medicaid	0 (0)	1 (9)	0 (0)	
Other/Unknown	15 (19)	3 (27)	20 (50)	
Socioeconomic status				
Low	3 (4)	1 (9)	1 (2)	
Medium	28 (36)	4 (36)	9 (23)	0.35
High	47 (60)	6 (55)	30 (75)	

SNHL = sensorineural hearing loss

Table 2

Neurodevelopmental assessments among case-patients with normal hearing or with sensorineural hearing loss by age 2 years and controls

Neurodevelopmental assessment	Case-patients with normal hearing (n=78)	Case-patients with SNHL (n=11)	Controls (n=40)
Full scale intelligence			
Number of children tested (%)	75 (96)	11 (100)	39 (98)
Median number of tests (IQR)	7 (5–8)	7 (6–8)	4 (2–5)
Median age at last assessment, years (IQR)	17.1 (14.5–17.5)	17.7 (17.4–18.3)	17.1 (14.6–17.6)
Verbal intelligence			
Number of children tested (%)	72 (92)	10 (91)	35 (88)
Median number of tests (IQR)	4 (3–4)	4 (4–4)	3 (2–4)
Median age at last assessment, years (IQR)	17.2 (15.8–17.6)	17.8 (17.5–17.9)	17.4 (16.6–17.7)
Non-verbal intelligence			
Number of children tested (%)	72 (92)	11 (100)	35 (88)
Median number of tests (IQR)	4 (3–4)	4 (3–4)	3 (2–4)
Median age at last assessment, years (IQR)	17.2 (15.8–17.6)	17.7 (17.4–17.9)	17.4 (16.6–17.7)
Receptive vocabulary			
Number of children tested (%)	72 (92)	11 (100)	35 (88)
Median number of tests (IQR)	3 (2–4)	4 (3–5)	2 (2–3)
Median age at last assessment, years (IQR)	17.1 (14.6–17.6)	17.7 (17.4–17.9)	17.2 (15.6–17.6)
Expressive vocabulary			
Number of children tested (%)	70 (90)	11 (100)	33 (83)
Median number of tests (IQR)	2.5 (2–3)	3 (2–3)	1 (1–2)
Median age at last assessment, years (IQR)	13.3 (10.1–13.7)	13.2 (11.3–13.6)	13.4 (12.3–14.1)
Academic achievement - Math			
Number of children tested (%)	70 (90)	11 (100)	35 (88)
Median number of tests (IQR)	3 (2–4)	3 (3–4)	2 (2–3)
Median age at last assessment, years (IQR)	17.2 (16.4–17.6)	17.7 (17.4–17.9)	17.4 (16.9–17.7)
Academic achievement - Reading			
Number of children tested (%)	70 (90)	11 (100)	35 (88)
Median number of tests (IQR)	3 (2–4)	3 (3–4)	2 (2–3)
Median age at last assessment, years (IQR)	17.2 (16.4–17.6)	17.7 (17.4–17.9)	17.2 (16.4–17.6)

SNHL = sensorineural hearing loss

IQR = interquartile range