Long-term outcomes of children with symptomatic congenital cytomegalovirus disease

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Abstract

Objective—To assess long-term outcomes of children with symptomatic congenital cytomegalovirus (CMV) disease detected at birth.

Methods—We used Cox regression to assess risk factors for intellectual disability (intelligence quotient <70), sensorineural hearing loss (SNHL; hearing level 25 dB in any audiometric frequency), and vision impairment (best corrected visual acuity >20 or based on ophthalmologist report).

Results—Among 76 case-patients followed through median age of 13 (range: 0–27) years, 56 (74%) had SNHL, 31 (43%, n=72) had intellectual disability, and 18 (27%, n=66) had vision impairment; 28 (43%, n=65) had intellectual disability and SNHL with/without vision impairment. Microcephaly was significantly associated with each of the three outcomes. Tissue destruction and dysplastic growth on head computed tomography scan at birth was significantly associated with intellectual disability and SNHL.

Conclusion—Infants with symptomatic congenital CMV disease may develop moderate to severe impairments, which were associated with presence of microcephaly and brain abnormalities.

Keywords

congenital cytomegalovirus; intellectual disability; sensorineural hearing loss; vision impairment

BACKGROUND

Congenital cytomegalovirus (CMV) infection can cause microcephaly and result in a spectrum of neurodevelopmental disorders, such as sensorineural hearing loss (SNHL), vision loss, and intellectual impairment.[1] In the United States, an estimated 20 000 (0.5%) children are born with congenital CMV infection annually[2, 3], of whom approximately 2 000–3 000 (10–15%) are symptomatic at birth, including 400 (2%) with microcephaly.[4, 5, 6, 7, 8, 9, 10, 11, 12] About 50–70% of children with symptomatic CMV disease at birth develop permanent sequelae.[1] Antiviral treatment has been shown to improve developmental outcomes and reduce progression of SNHL in children with neurologic complications of congenital CMV disease at birth.[13, 14] However, because disease symptoms at birth may be mild or non-specific, it is likely that only a minority of children with symptomatic congenital CMV disease are clinically diagnosed in the absence of newborn screening.[15] Thus, the full impact of congenital CMV disease throughout the course of childhood remains largely unrecognized. Furthermore, the varying definitions of symptomatic congenital CMV disease complicates comparisons across studies.[16, 17] In the present study, we describe neurodevelopmental, hearing, and vision outcomes of children with symptomatic congenital CMV disease detected at birth followed through a median age of 13 years.

METHODS

Our study included 76 children born during 1983–2005 who were enrolled in the Congenital CMV Longitudinal Study[11, 18, 19] as case-patients with confirmed symptomatic congenital CMV disease, defined as a newborn with CMV infection detected by culture of urine samples collected within 3 weeks of life who presented at least one of the following CMV-related signs at birth: purpura/petechiae, jaundice, hepatosplenomegaly, microcephaly, unexplained neurological abnormality, elevated liver enzymes (alanine aminotransferase >100 IU), hyperbilirubinemia (total bilirubin >3mg/dl), hemolytic anemia, or thrombocytopenia (platelet count <75 000/mm^3). We did not consider infants who were small for gestational age (SGA) or had congenital SNHL in the absence of at least one of the above signs as having symptomatic congenital CMV disease.[16] Seventy-three (95%) case-patients were referrals from several hospitals, and 4 (5%) case-patients were identified by routine newborn CMV screening at Women's Hospital of Texas, Houston TX, where the observed CMV birth prevalence was 0.4% (135 CMV-positive infants among 32 543 screened during 1982–1992)[19]. Ninety-six (71%) CMV-positive newborns whose parents provided consent were enrolled in the Congenital CMV Longitudinal Study, 4 (4%) were case-patients included in the present analysis, and 92 (96%) were asymptomatic at birth for

whom hearing outcomes have been previously described.[19] Case-patients had neuroimaging evaluations performed by head computed tomography (CT) scans within 4 months of age, and were followed with neurodevelopmental, hearing and ophthalmologic evaluations during infancy, pre-school, elementary, middle, and high school years. The Institutional Review Board for Human Subject Research for Baylor College of Medicine and Affiliated Hospitals approved the study protocol.

We describe case-patients by demographic characteristics, CMV-related signs at birth, and other clinical characteristics, including pre-term birth and SGA. We categorized case-patients as SGA or having microcephaly in two ways - based on physicians' clinical assessment at birth and defining SGA as birth weight ≤10th percentile and microcephaly as fronto-occipital head circumference ≤3rd and ≤10th percentiles, using the Olsen's intrauterine growth curves.[20] We classified abnormal head CT findings in infancy into three broad categories implying 1) tissue destruction (calcification, hemorrhage, stroke, encephalomalacia, white matter lucency, porencephaly/cysts, or atrophy); 2) attenuated growth (immaturity, hypoplasia, or underopercularization); and 3) dysplastic growth (migrational abnormalities, such as lissencephaly or pachygyria). Volume loss was inferred by dilatation of cisterns and/or cerebrospinal fluid spaces.

Neurodevelopmental evaluations included assessments of physical, motor, sensory, and cognitive development in infants and young children, and measurement of intelligence quotient or adaptive level of functioning among older children. Neurodevelopmental evaluation was done using one of the following tests: Bayley Scales of Infant Development[21] (n=13), McCarthy Scales of Children's Abilities[22] (n=4), Wechsler Intelligence Scale for Children - 3rd edition[23] (n=4), Wechsler Abbreviated Scale of Intelligence[24] (n=23), Kaufman Assessment Battery for Children[25] (n=7), Leiter International Performance Scale – Revised[26] (n=2), Stanford Binet Intelligence Scale[27] (n=2), and Vineland Adaptive Behavior Scales[28] (n=18). All tests have scores standardized to a mean of 100 with a standard deviation of 15 or 16, allowing us to combine the scores from case-patients assessed at different ages using different instruments. For the 3 case-patients who received the Bayley Scales of Infant Development at the last evaluation at ≥42 months of age, we calculated the IQ based on the age-equivalent scores divided by the age at the time of testing multiplied by 100. We categorized case-patients as having intellectual disability, borderline intelligence, and normal intelligence when standard scores at last evaluation were <70, 70–84, and ≥85, respectively.[29]

Hearing evaluations included click and tone-burst auditory brainstem response (ABR), behavioral audiometry from 0.25 to 8 kHz, and tympanometry. We defined SNHL as ≥25 dB hearing level for the click ABR or at any frequency for the corrected tone-burst or pure-tone air conduction results, in the absence of middle ear disorder. We categorized SNHL for each ear as congenital/early-onset when detected in the first ABR assessment at age ≤12 months and confirmed in subsequent assessments, or as delayed-onset when detected after one or more assessments with normal hearing. We also categorized SNHL by laterality and severity, as previously described.[19]

Ophthalmologic evaluations included external ocular exam, indirect ophthalmoscopy, and measurement of best corrected visual acuity (Snellen score) in older children or assessment of fixation behavior in nonverbal and preverbal children. We defined an ophthalmic abnormality as any of the following conditions: chorioretinitis, optic nerve atrophy, strabismus (including esotropia or exotropia), nystagmus, amblyopia, or astigmatism. Based on the last ophthalmologic visit, we categorized case-patients as having normal vision (20), mild/moderate vision impairment (21–69), low vision (70–199), and legal blindness (200), using the Snellen scores in the better eye, or based on the ophthalmologist assessment for nonverbal and pre-verbal children.[30]

Using the Cox proportional hazards regression model and the Firth method to reduce small sample size bias[31], we calculated hazard ratios (HR) and 95% confidence intervals (CI) to assess whether selected clinical signs at birth (petechiae/purpura, jaundice or hyperbilirubinemia, hepatosplenomegaly, microcephaly, SGA, or pre-term birth) or abnormal head CT findings (tissue destruction, attenuated growth, or dysplastic growth) within 4 months of birth were predictors for intellectual disability, SNHL, ophthalmic abnormality, or vision impairment. For the models, we defined microcephaly as head circumference 3rd percentile and SGA as birth weight 10th percentile. We did not combine clinical signs at birth with head CT findings as predictors in the same model because they were potentially correlated with each other. We considered results with a p-value <0.05 as statistically significant. For analyses, we used SAS version 9.3 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Demographic and clinical characteristics at birth

Of the 76 case-patients, 55 (72%) were born during 1983–1998, before establishment of the Texas Newborn Hearing Screening Program in 1999, and 21 (28%) during 1999–2005. The majority of case-patients were born to mothers who were <25 years of age (62%), non-Hispanic White (57%), married (60%), primipara (52%) and who had no other living children at the time of birth (59%).

Thirty-five (46%) case-patients were males and 52 (68%) were born at term. Fifty-nine (78%) case-patients had urine samples for CMV testing collected within 3 days of life, and 17 (22%) between 4–21 days of life. The most common CMV-related signs present at birth were petechiae/purpura (72%) and thrombocytopenia (70%) (Table 1). A greater proportion of case-patients were SGA based on the Olsen's intrauterine growth curves than based on physician's clinical assessment at birth (58% vs. 37%). The proportion of case-patients with microcephaly was 41%, based on physician's clinical assessment at birth. Among 73 case-patients with head circumference measurement recorded, 34% had head circumference 3rd and 51% 10th percentile for gestational age. The median age at last follow-up visit was 13 (range: 0–27) years. Eight case-patients died during the follow-up period; 1 (1.3%) at age 2 months, 2 (2.6%) at 2 years, 3 (3.8%) at 12–13 years, and 2 (2.6%) at 20 years. One case-patient who died had a diagnosis of sudden infant death syndrome, 4 had respiratory failure (1 at age 2 years and 3 at ages 12–13 years), 2 had post-surgical complications (ages 2 and 20 years), and 1 had an accidental drug overdose (age 20 years).

Head computed tomography scan findings

Seventy-three case-patients had a head CT performed within the first 4 months of life, at a median age of 8 days (range 0–4 months). A total of 62 (85%) case-patients had abnormal findings, categorized as tissue destruction in 49 (67%), attenuated growth in 21 (29%), and dysplastic growth in 6 (8%) (Table 1). The most common abnormal findings were intracranial calcifications, ventricular dilatation, and white matter lucency, observed in 43 (59%), 40 (55%), and 20 (27%) case-patients, respectively. Volume loss was observed in 34 (69%) case-patients with tissue destruction, in 12 (57%) with growth attenuation, and in 5 (83%) with dysplastic growth. In univariate analyses, microcephaly at birth was significantly associated with tissue destruction and dysplastic growth shown by head CT; pre-term birth was significantly associated with attenuated growth shown by head CT ($p < 0.05$).

Neurodevelopmental, hearing and vision outcomes

Among 72 case-patients with a neurodevelopmental evaluation, the median age at the last evaluation was 10 (range: 0.4–27) years. Thirty-one (43%) case-patients had intellectual disability, 12 (17%) had borderline intelligence, and 29 (40%) had normal intelligence (Table 1). Among 31 case-patients with intellectual disability, the median intelligence score was 35 (range: 5–67) and the median verbal score was 33 (range: 20–74). Among 12 case-patients with borderline intelligence, the median intelligence score was 82 (range: 70–84), and the median verbal score was 78 (range: 72–97). Of 29 case-patients with normal intelligence, the median intelligence score was 106 (range: 85–122), and the median verbal score was 105 (range: 84–120).

Among 76 case-patients with an audiologic evaluation, the median age at first evaluation was 18 days (range: 4 days–8 years); 75 case-patients were first evaluated within 10 months of birth. Overall, 56 (74%) case-patients had SNHL (Table 1), among whom 44 (79%) had congenital/early-onset SNHL and 12 (21%) developed delayed-onset SNHL detected at a median age of 3 (range: 0.5–11) years. Forty-seven (84%) case-patients with SNHL had bilateral loss, of which 38 (81%) had bilateral loss at first diagnosis, and 9 (19%) were initially diagnosed with unilateral loss, but developed delayed-onset SNHL in the contra-lateral ear. The median interval from unilateral to bilateral loss was 3 months (range: 7 days–5 years) among 5 case-patients who initially presented with unilateral congenital/early-onset SNHL, and 4 years (range: 3–6 years) among 4 case-patients who presented with unilateral delayed-onset SNHL.

Most case-patients with SNHL had moderate to profound SNHL since infancy and SNHL severity worsened with age. At first assessment, 44% of all case-patients with SNHL and 32% of those with bilateral SNHL had profound loss in the poorer- and better-hearing ears, respectively. At last assessment, 61% of all case-patients with SNHL and 57% of those with bilateral SNHL had profound loss in the poorer- and better-hearing ears. Thirty-five (63%) of 56 case-patients with SNHL received hearing aids, among whom 26 (74%) received bilateral hearing aids. A total of 15 (27%) case-patients received cochlear implants, including 10 who initially used hearing aids. Five (33%) received the first cochlear implant by age 2 years, 6 (40%) between 3–7 years, and 4 (27%) at 14 years. Five case-patients

received cochlear implants bilaterally, among whom the second implantation was done at a median of 2 (range: 1–5) years after the first.

Among 76 case-patients, 39 (51%) had an ophthalmic abnormality, including 19 (25%) with chorioretinitis and 9 (12%) with optic nerve atrophy (Table 1). Overall, among 66 (87%) case-patients with vision evaluation, 44 (67%) had normal vision, 8 (12%) had mild/moderate vision impairment, 4 (6%) had low vision, and 10 (15%) had legal blindness. Among 41 (54%) case-patients with a Snellen score for both eyes, including 12 (29%) with correction, 32 (78%) had normal vision, 8 (20%) had mild/moderate vision impairment, and 1 (2%) had low vision. Among 25 (33%) case-patients without a Snellen score in both eyes, 12 (48%) had normal vision, 3 (12%) had low vision, and 10 (40%) had legal blindness.

Overall, among 65 (86%) case-patients with neurodevelopmental, hearing and vision evaluations, 28 (43%) had intellectual disability and SNHL with or without vision impairment, 2 (3%) had intellectual disability with normal hearing and vision, and 16 (25%) had borderline/normal intelligence with moderate to profound SNHL in the better-hearing ear (1 of whom had legal blindness, and 2 with mild/moderate vision impairment). The remaining 19 (29%) case-patients had borderline/normal intelligence, of whom 7 had moderate to profound SNHL in the poorer-hearing ear, 2 had mild/moderate vision impairment, and 10 had normal hearing and vision.

Predictors of intellectual disability, SNHL, ophthalmic abnormalities, and vision impairment

In multivariate analysis of clinical signs at birth, microcephaly was significantly associated with intellectual disability (HR: 3.4, 95% CI: 1.5–7.6), SNHL (HR: 2.6, 95% CI: 1.4–5.0), ophthalmic abnormality (HR: 2.7, 95% CI: 1.2–6.0), and vision impairment (HR: 6.4, 95% CI: 1.6–26.4) (Table 2). Petechiae/purpura were associated with decreased risk of SNHL (HR: 0.4, 95% CI: 0.2–0.8), while hepatosplenomegaly was associated with increased risk of SNHL (HR: 3.4, 95% CI: 1.6–7.3). Jaundice was associated with a decreased risk of vision impairment (HR: 0.2, 95% CI: 0.1–0.8). In multivariate analyses of head CT findings, tissue destruction was significantly associated with intellectual disability (HR: 4.2, 95% CI: 1.1–16.1) and SNHL (HR: 2.2, 95% CI: 1.1–4.3). Dysplastic growth was significantly associated with intellectual disability (HR: 4.4, 95% CI: 1.7–11.5), SNHL (HR: 2.4, 95% CI: 1.0–5.8), ophthalmic abnormalities (HR: 6.1, 95% CI: 2.3–16.6), and vision impairment (HR: 10.4, 95% CI: 2.9–37.7). Neither pre-term birth nor attenuated growth shown by head CT were significantly associated with intellectual disability, SNHL, ophthalmic abnormalities or vision impairment (p>0.05).

DISCUSSION

In this longitudinal study of children with confirmed symptomatic congenital CMV disease, the majority of whom were clinically referred, we observed a high proportion of case-patients with microcephaly, intellectual disability, SNHL, ophthalmic abnormalities and vision impairment. Among case-patients with intellectual disability, the median intelligence score was in the severe to profound range, suggesting that a substantial proportion of these children likely require daily supervision, help with self-care activities, and special education,

in addition to long-term monitoring and health interventions. It is likely that a greater proportion of children with symptomatic congenital CMV disease identified through referrals have more severe manifestations at birth and disabilities than those who would be identified through newborn screening.[32] Thus, our data should not be generalized to all infants with congenital CMV infection, among whom only 10–15% present with symptomatic disease of varying degree of severity at birth. We found the prevalence of moderate to severe outcomes was 71% among our case-patients in contrast to the 32% found among infants with congenital CMV infection identified in 2 large population-based newborn screening studies.[33] We did not include congenital SNHL as a defining condition for symptomatic congenital CMV disease which if we had would have resulted in a greater number of infants classified as having symptomatic infection and a lower estimate of the proportion with intellectual disability.

We found microcephaly was significantly associated with abnormal head CT findings indicative of tissue destruction and dysplastic growth, as well as intellectual disability, SNHL, ophthalmic abnormalities and vision impairment. Our findings expand on a previous analysis of 41 case-patients from our cohort, reinforcing the specificity of microcephaly as a predictor of poor cognitive outcome.[34] None of the case-patients in our study with normal intelligence, hearing, and vision had microcephaly at birth. In newborn screening studies, the proportion of children with symptomatic congenital CMV disease who have microcephaly ranges between 7–40%.[4, 5, 6, 7, 8, 9, 10, 11, 12] Many of these studies used the 10th percentile as a cutoff for microcephaly, hence, the prevalence of microcephaly may have been overestimated. In our study, using the 3rd percentile for head circumference adjusted for gestational age at birth, we found 34% of case-patients had microcephaly, lower than the 40% classified by physician report. Using standardized methods to assess microcephaly in infants with congenital CMV infection is important, not only to allow comparability across studies, but to accurately inform clinical management decisions and inform prognosis.

Although head CT abnormalities have been associated with impairments/disabilities in children with symptomatic congenital CMV disease, the types of abnormalities that predict adverse outcomes have not been assessed.[35] We found that tissue destruction and dysplastic growth were significantly associated with microcephaly at birth, intellectual disability and SNHL. Dysplastic growth was also associated with ophthalmic abnormalities and vision impairment. Currently, it is recommended that CT be limited to selected cases because exposure to ionizing radiation may affect the developing human brain. More recently, neuroimaging using magnetic resonance, which was not available for our cohort, and ultrasound, have been recommended for the diagnosis and categorization of brain developmental disorders and white matter disease, including for children with asymptomatic congenital CMV infection.[36, 37, 38] Severe brain abnormalities very similar to those of our case-patients with symptomatic congenital CMV disease have been recently reported in cases of microcephaly associated with congenital Zika virus infection.[39] Development of standard clinical and diagnostic protocols, including neuroimaging evaluations, would be needed should newborn screening for congenital CMV infection be implemented. Our findings from head CT suggest that tissue destruction or dysplastic growth shown by magnetic resonance or ultrasound would be useful to inform prognosis of affected children.

In our study, the majority of case-patients had moderate to profound SNHL since early infancy and received hearing device interventions, including hearing aids and cochlear implants. The first cochlear implantation among our case-patients was performed in 1998. Twice as many children who received cochlear implants in our study would likely have met the current candidacy criteria for cochlear implantation. Data from small studies have shown that children with congenital CMV-related SNHL may benefit from cochlear implantation but perform less well than a comparable group of children with implants who do not have congenital CMV infection; this lag may be related to the degree of CMV-related motor or cognitive disabilities.[40, 41, 42, 43] Children who receive cochlear implants require ongoing audiological and otolaryngological follow-up, as well as training/rehabilitation to develop a wide range of listening skills for optimal benefit from their devices.[44] More data on quality of life, language skills and educational achievement following cochlear implantation in children with congenital CMV-related SNHL will be useful to document potential benefits and provide realistic expectations to patients and parents considering this intervention.

Vision impairment in children with symptomatic congenital CMV disease may be caused by cortical, optic nerve, and/or retinal abnormalities.[45] Data on long-term vision outcomes for children with congenital CMV infection are limited.[1] Overall, 21% of our case-patients had low vision or legal blindness. In our study, half of case-patients had an ophthalmic abnormality; 25% had chorioretinitis, not much higher than in previous reports.[32] Among case-patients with vision evaluation, 55% of those with chorioretinitis and/or optic nerve atrophy had at least mild/moderate vision impairment, consistent with the 58% reported in another study.[46] The evidence suggests that infants with symptomatic congenital CMV disease should receive careful ophthalmologic screening and regular follow-up examinations to allow for early intervention.[45, 47]

Our study had some limitations. Clinical data for CMV-positive newborns that were identified by routine CMV screening but not enrolled in the study were not available. Although we estimate only 2–3 of these newborns would have presented with symptomatic disease at birth, those who died in the neonatal period would not have had the opportunity to be enrolled in the study. In our cohort, the cumulative mortality rate within 2 years of life was 4%, comparable to that of 5–6% reported in previous studies.[1, 32] Although a few case-patients were born pre-term, we found no significant association of pre-term birth or head CT findings suggesting prematurity with any of the severe outcomes. Because case-patients were born over the course of 2 decades, the available diagnostic procedures, treatment and interventions evolved over time. We did not investigate all clinically important outcomes, including outcomes such as cerebral palsy and nutritional status, or interventions that these children required or received, such as orthopedic surgeries, assistive devices, and physical, occupational, speech and language therapies. Additionally, we were unable to report on the impact on quality of life of affected children and families, which should be included for more complete assessment of burden of disease and its economic impact.

Determining the burden of disease associated with congenital CMV infection is critical to assess the cost-effectiveness of newborn screening for congenital CMV infection. The severity of outcomes vary widely and the data available on the range of disabilities among affected children are limited.[16, 48, 49] Our study provides detailed outcome data for a subset

of congenitally infected infants that were diagnosed at birth and likely overestimates the burden of disease among all children with congenital CMV infection that is symptomatic at birth. More data on the prevalence and spectrum of long-term outcomes among both symptomatic and asymptomatic infants are needed to estimate the potential benefit and assess the cost-effectiveness of newborn screening for congenital CMV infection.

In the United States, symptomatic congenital CMV disease is estimated to affect approximately 2 000–3 000 newborns annually. An additional 900 infants with asymptomatic congenital CMV infection are estimated to have SNHL within 8 weeks of life, although nearly half of these infants are likely missed by newborn hearing screening.[50] Children with delayed-onset SNHL occurring during the first 9 months of age are likely to benefit from early intervention.[16] By age 5 years, 360 (2%) of children with asymptomatic congenital CMV infection are estimated to have severe enough bilateral SNHL to potentially meet candidacy criteria for cochlear implantation.[19] A laboratory-confirmed diagnosis of congenital CMV disease in the first month of life is critical for implementing appropriate clinical management, including administration of antivirals for eligible infants.[13, 14] Most cases of symptomatic congenital CMV disease likely remain undiagnosed because they present with mild or non-specific signs.[15, 51] Although congenital CMV infection meets some of the criteria for inclusion in the newborn screening panel, more research is needed to develop a screening test appropriate for large scale implementation, inform guidelines for treating and monitoring children with congenital CMV infection, and assess the cost-benefit or cost-effectiveness of CMV screening.[52, 53]

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Contributor's Statement

Tatiana M. Lanzieri conceptualized and conducted analysis contained in this report, interpreted the data, led the writing of the initial manuscript and revised versions, and approved the final version.

Jessica Leung conducted analysis contained in this report, interpreted the data, revised the manuscript and approved the final version.

Winnie Chung conceptualized the analysis contained in this report, reviewed and interpreted individual audiological data, revised the manuscript and approved the final version.

Marily Flores and Jerry A. Miller assisted with data management and quality control for the Longitudinal Congenital CMV Study, revised the manuscript and approved the final version.

Peggy Blum conceptualized and provided audiological follow-up in the Longitudinal Congenital CMV Study, revised the manuscript and approved the final version.

A. Chantal Caviness was the co-Principal Investigator for the Longitudinal Congenital CMV Study, revised individual clinical, laboratory and head computed tomography data, conducted analysis contained in this report, 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.

Sherry S. Vinson, Marie R. Turcich, and Robert G. Voigt conducted the neurodevelopmental evaluations, 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, conceptualized the analysis contained in this report, interpreted the data, revised the manuscript and approved the final version.

Abbreviations

ABR	auditory brainstem response
CI	confidence interval
CMV	cytomegalovirus
CT	computed tomography
HR	hazard ratio
SGA	small for gestational age
SNHL	sensorineural hearing loss

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Table 1

Clinical characteristics at birth, head CT findings and long-term neurodevelopmental, hearing, and vision outcomes among children with symptomatic congenital CMV disease (n=76)

Characteristic	n (%)
Clinical signs during neonatal period	
Petechiae/purpura	55 (72)
Jaundice	30 (39)
Hepatosplenomegaly	38 (50)
Seizures	5 (7)
Small for gestational age	
Physician clinical assessment at birth	28 (37)
Birth weight <10th percentile [*]	44 (58)
Microcephaly	
Physician clinical assessment at birth	31 (41)
Head circumference 3rd percentile [*] (n=73)	25 (34)
Head circumference 10th percentile [*] (n=73)	37 (51)
Laboratory abnormalities	
Elevated alanine transaminase (>100 IU) (n=70)	12 (17)
Thrombocytopenia (Platelet count <75,000/mm3) (n=71)	50 (70)
Hyperbilirubinemia (Total bilirubin > 3mg/dl) (n=74)	28 (38)
Hemolytic anemia	3 (4)
Head CT findings (n=73)	
Intracranial calcifications	43 (59)
Ventricular dilatation	40 (55)
White matter lucency	20 (27)
Any abnormal finding	62 (85)
Broad categories	
Tissue destruction	49 (67)
Attenuated growth	21 (29)
Dysplastic growth	6 (8)
Neurodevelopmental outcomes (n=72)	
Intellectual disability	31 (43)
Borderline intelligence	12 (17)
Normal intelligence	29 (40)
Hearing outcomes	
SNHL	56 (74)
Normal hearing	20 (26)
SNHL onset (n=56)	
Congenital/early-onset SNHL	44 (79)
Delayed-onset SNHL	12 (21)

Characteristic	n (%)
Laterality (n=56)	
Bilateral SNHL	47 (84)
Unilateral SNHL	9 (16)
Severity (n=47) [**]	
25 dB in isolated frequency	1 (2)
Slight (16 – 25 dB)	5 (11)
Mild (26 – 40 dB)	2 (4)
Moderate (41 – 55 dB)	4 (9)
Moderately severe (56 – 70 dB)	1 (2)
Severe (71 – 90 dB)	7 (15)
Profound (>90 dB)	27 (57)
Ophthalmic abnormalities	
Astigmatism	22 (29)
Strabismus	19 (25)
Nystagmus	11 (14)
Amblyopia	3 (4)
Chorioretinitis	19 (25)
Optic nerve atrophy	9 (12)
Any ophthalmic abnormality	39 (51)
Vision outcomes (n=66)	
Normal vision	44 (67)
Mild/moderate vision impairment	8 (12)
Low vision	4 (6)
Legal blindness	10 (15)

[*]
Based on Olsen's intrauterine growth charts

[**]
Better-hearing ear at the last assessment

Table 2

Multivariate Cox proportional hazards regression analysis of CMV-related clinical signs at birth and head computed tomography scan findings and neurodevelopmental outcomes, hearing loss, vision abnormalities, and vision impairment

	Intellectual disability		Sensorineural hearing loss		Ophthalmic abnormality		Vision impairment	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Model 1 (Clinical signs at birth)	(n=65)		(n=70)		(n=70)		(n=61)	
Petechiae/purpura	1.2 (0.4–3.5)	0.690	0.4 (0.2–0.8)	0.011	1.2 (0.5–3.1)	0.697	1.6 (0.4–7.3)	0.523
Jaundice or hyperbilirubinemia	0.6 (0.3–1.4)	0.289	1.0 (0.5–1.8)	0.987	0.6 (0.3–1.2)	0.140	0.2 (0.1–0.8)	0.024
Hepatosplenomegaly	1.8 (0.7–4.4)	0.218	3.4 (1.6–7.3)	0.002	1.2 (0.5–2.9)	0.618	0.7 (0.2–2.4)	0.593
Microcephaly at birth[a]	3.4 (1.5–7.6)	0.003	2.6 (1.4–5.0)	0.004	2.7 (1.2–6.0)	0.019	6.4 (1.6–26.4)	0.010
Small for gestational age[b]	1.5 (0.6–3.5)	0.386	1.1 (0.6–2.2)	0.759	1.6 (0.7–3.6)	0.290	1.9 (0.5–7.5)	0.373
Pre-term birth[c]	1.3 (0.6–3.0)	0.498	1.0 (0.5–1.7)	0.902	1.7 (0.8–3.6)	0.136	2.1 (0.6–7.1)	0.241
Model 2 (Head computed tomography scan findings within 4 months of age)	(n=68)		(n=73)		(n=73)		(n=64)	
Destruction	4.2 (1.1–16.1)	0.036	2.2 (1.1–4.3)	0.024	2.1 (0.9–4.8)	0.077	15.7 (0.8–303.1)	0.068
Attenuated growth	1.0 (0.4–2.1)	0.914	1.6 (0.8–2.9)	0.154	1.6 (0.8–3.3)	0.165	1.9 (0.6–5.9)	0.237
Dysplastic growth	4.4 (1.7–11.5)	0.002	2.4 (1.0–5.8)	0.042	6.1 (2.3–16.6)	<0.001	10.4 (2.9–37.7)	<0.001

HR=hazard ratio, CI=confidence interval

[a] Microcephaly defined as head circumference <3rd percentile for gestational age

[b] Small for gestational age defined as birth weight 10th percentile

[c] Pre-term birth defined as birth before 37 weeks gestational age