



Evaluation of clinically asymptomatic high risk infants with congenital cytomegalovirus infection

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Abstract

Objective To determine the frequency of abnormal findings on evaluation of neonates with congenital CMV infection who have a normal physical examination

Study design Retrospective, 2-center study (1996–2017) that reviewed results of complete blood cell count and platelets, serum alanine aminotransferase (ALT) and bilirubin concentrations, eye examination, cranial ultrasonography or other neuroimaging, and brainstem evoked responses performed on neonates with congenital CMV infection and a normal physical examination

Results Of 34 infants with congenital CMV infection and a normal physical examination, 56% (19/34) had ≥ 1 abnormality: 39%, elevated ALT concentration; 45%, abnormal neuroimaging (five, lenticulostriate vasculopathy; six, intraventricular hemorrhage; four, calcifications); 12%, anemia; 16%, thrombocytopenia; and 3%, chorioretinitis. Seven (21%) infants had sensorineural hearing loss, and 18 infants received antiviral therapy.

Conclusion Some infants with congenital CMV infection and a normal physical examination had abnormalities on laboratory or neuroimaging evaluation, which in some cases prompted antiviral treatment.

Introduction

Congenital cytomegalovirus (CMV) infection occurs in 0.2–2.4% of all live births and is a leading nongenetic cause of sensorineural hearing loss and neurodevelopmental

impairment in childhood [1–6]. Approximately 90% of neonates with congenital CMV infection are “asymptomatic,” meaning that they are well-appearing and have no clinically apparent signs of disease detected at birth. Since these infants have a normal physical examination, they often are not evaluated with laboratory or neuroimaging studies. In some cases, abnormalities detected on such tests, if performed, may reclassify them as “symptomatic,” thereby increasing the risk of hearing loss and disabilities from the 5 to 10% seen in asymptomatic infants [7, 8].

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Moreover, recognition of abnormalities may identify neonates who could benefit from antiviral therapy. However, it remains unknown how often neonates with clinically inapparent CMV infection have subtle abnormalities detected on more complete evaluation. Therefore, the objective of this study was to determine the frequency of abnormal findings on laboratory, ophthalmologic, neuroimaging, and audiologic evaluation performed on neonates who had a normal physical examination and were diagnosed with congenital CMV infection, the majority of which occurred in the setting of recognized primary maternal infection.

Materials and methods

This was a retrospective cohort study of prospectively collected data on infants with congenital CMV infection who were referred to and evaluated by the authors at Parkland Memorial Hospital and Children's Medical Center, Dallas, TX from 1996 to 2011 (PJS) and at Clinica y Maternidad Suizo Argentina, Sanatorio Otamendi, Stamboulion Center, and Sanatorio de la Trinidad Ramos Mejía, Buenos Aires, Argentina from 2008 to 2017 (FG and LNV). Congenital CMV infection was defined as a positive culture or polymerase chain reaction (PCR) test of urine performed in the first 21 days of age [9, 10]. The study was approved by the Institutional Review Board of the University of Texas Southwestern Medical Center with written or verbal consent obtained from parents of infants enrolled at the participating centers in Buenos Aires, Argentina.

Infants with congenital CMV infection who had a normal physical examination and growth parameters constituted the study population. They were identified by targeted CMV screening when born to mothers who seroconverted for CMV during pregnancy or were infected with the human immunodeficiency virus (HIV), there was a sibling with congenital CMV infection, or they failed the newborn hearing screen [11–13]. The infants' medical records were reviewed and pertinent demographic, clinical, laboratory, and radiographic data were recorded. Specifically, the results of the complete blood cell count (CBC) and platelets, serum alanine aminotransferase (ALT) concentration, serum bilirubin (total/direct) concentration, eye examination, cranial ultrasonography or other neuroimaging, and brainstem evoked responses (BSER) from the initial presentation or evaluation were reviewed.

Definitions

For term newborns born at ≥ 37 weeks' gestation and preterm newborns born at < 37 weeks' gestation, serum ALT ≥ 40 U/mL and direct bilirubin > 2 mg/dL were considered abnormal. Anemia was defined as hematocrit $< 40\%$ at

0–7 days of age, $< 35\%$ at 8–14 days, and $< 30\%$ at 15–28 days, and thrombocytopenia as a platelet count of $< 150,000/\text{mm}^3$ [14]. BSER threshold of 0–20 dB was considered normal hearing, while thresholds of 21–30, 31–60, and 61–90 dB constituted mild, moderate, and severe hearing loss, respectively [15].

Statistical analysis

Statistical analysis was performed using Sigma Plot 11.0 (SPSS, Chicago, IL) and GraphPad Software (San Diego, CA). Descriptive analyses were performed using frequency distributions and rates. Means with standard deviation (SD) and medians were used to summarize patient demographics and characteristics, where appropriate.

Results

During the study period, there were 34 infants who had a normal physical examination and were diagnosed with CMV infection by culture ($n = 14$, Dallas) or PCR testing ($n = 20$, Buenos Aires) of urine performed in the first 3 weeks of age. The majority (82%) of the mothers were Hispanic and delivered vaginally (68%); 15% (5/34) of the infants were preterm and 63% were male (Table 1). Infants were diagnosed with CMV infection for the following reasons: 3 (9%) had mothers with HIV infection although none of the infants were infected, 21 (62%) had mothers diagnosed with CMV infection during the pregnancy, 6 (18%) referred on the newborn hearing screen, 1 (3%) had a sibling with congenital CMV infection, and 3 (9%) were preterm who had abnormalities detected as part of standard medical care. Of the latter three preterm infants, one born at 29 weeks' gestation had thrombocytopenia and abnormal cerebral ultrasound, one born at 33 weeks' gestation had thrombocytopenia, and one born at 27 weeks' gestation had abnormal cerebral ultrasound (Table 1).

Of the 21 mothers diagnosed with CMV infection during the pregnancy, two mothers of infants at Parkland Hospital and Children's Medical Center, Dallas, had fever and upper respiratory tract infection and both had serum CMV IgM and IgG antibodies detected in the second or third trimester, with one having a negative blood CMV DNA PCR test. Neither mother received any CMV-specific treatment. The other 19 mothers were from Buenos Aires and had serum CMV IgM and IgG antibodies detected during pregnancy as part of standard prenatal care, with one of them also having a positive blood CMV PCR test, and 12 had an amniocentesis that resulted in a positive amniotic fluid CMV DNA PCR test. Nine of the women had flu-like symptoms during pregnancy, and 12 received hyperimmune CMV immune globulin intravenous therapy in Buenos Aires.

Table 1 Characteristics of the mothers and their infants who had congenital CMV infection and a normal physical examination

	Dallas	Buenos Aires	Total
No. of mothers	14	20	34
Age (year, mean \pm SD, range)	25.8 \pm 5.7 (17–33)	33.1 \pm 8 (22–52)	29.9 \pm 6.9 (17–52)
Ethnicity			
Hispanic	8 (57%)	20 (100%)	28 (82%)
Non-Hispanic white	5 (36%)	0	5 (15%)
Non-Hispanic black	1 (7%)	0	1 (3%)
Type of delivery ($n = 28$)			
Vaginal	9 (64%)	10/14 (71%) ^a	19 (68%)
Cesarean	5 (36%)	4/14 (29%) ^a	9 (32%)
CMV infection during pregnancy (positive serum CMV IgM and IgG; see text)	2	17	19
HIV-infection	3 (21%) ^b	0	3/31 (10%) ^a
No. of infants			
Age at diagnosis (days, mean \pm SD; range)	4.5 \pm 5.3 (1–21)	5.6 \pm 5.7 (1–21)	5.1 \pm 5.4 (1–21)
Gestational age (weeks, mean \pm SD; range)	37 \pm 3.4 (29–41)	37.9 \pm 3.1 (27–40)	37.4 \pm 3.2 (27–41)
Weight (gram, mean \pm SD; range)	2964 \pm 850 (860–4130)	2861 \pm 755 (1216–4045)	2900 \pm 792 (860–4130)
Head circumference (cm, mean \pm SD; range)	33.7 \pm 3.3 (25.5–39.5)	33.6 \pm 2.7 (27.5–38)	33.6 \pm 2.9 (25.5–39.5)
Male gender	6 (43%)	16 (80%)	22 (63%)

CMV cytomegalovirus, SD standard deviation, PCR polymerase chain reaction, HIV human immunodeficiency virus, cm centimeter

^aNumber positive/number tested or known

^bInfants not HIV-infected

Among the 34 CMV-infected neonates who had a normal physical examination, 19 (56%) had at least one abnormality on laboratory, radiographic, or ophthalmologic evaluation (Table 2) and eight (24%; 4, preterm) infants had ≥ 2 abnormalities. Laboratory testing performed on 25 (71%) infants revealed an elevated ALT concentration in 39% (9/23) of infants, two of whom also had lenticulostriate vasculopathy on cranial ultrasound with normal hearing, one had a grade I intraventricular hemorrhage and severe unilateral sensorineural hearing loss, one had periventricular and temporal lobe hyperlucency on brain magnetic resonance imaging (MRI) and normal hearing testing, while the remainder only had isolated elevation of ALT (Table 2). Anemia was detected in 12% (3/25) of infants, one of whom also had thrombocytopenia, one had lenticulostriate vasculopathy detected by cranial ultrasonography that was confirmed by MRI, and one had grade III–IV intraventricular hemorrhage detected by cranial ultrasonography.

Twenty-four (71%) neonates had neuroimaging performed that consisted of cranial ultrasonography ($n = 22$), computerized tomography ($n = 2$), or MRI ($n = 7$) (Table 2), with only four infants having more than one neuroimaging study (Table 3). Of the 22 infants who had a cranial ultrasound performed, ten (45%) had at least one abnormality, with lenticulostriate vasculopathy detected in five (23%) and grade I intraventricular hemorrhage in five (23%) infants (Tables 2, 3). One (5%) infant had both lenticulostriate vasculopathy and grade I intraventricular hemorrhage and another one (5%) had three abnormalities

consisting of ventriculomegaly, diffuse calcifications, and grade I intraventricular hemorrhage.

Cranial computerized tomography was performed in two infants and was abnormal in one that showed thalamic calcifications. The cranial ultrasound performed on the latter infant showed lenticulostriate vasculopathy (Table 3, infant #3). Brain MRI was performed in seven infants and was abnormal in three infants, with one having periventricular calcifications and temporal lobe hyperlucency (Table 3; patient #4, cranial ultrasound normal), one had thalamic calcifications (Table 3; patient #2; cranial ultrasound showed lenticulostriate vasculopathy), and another had germinal matrix hemorrhage (Table 3; patient #1, cranial ultrasound showed grade I intraventricular hemorrhage).

Ophthalmologic evaluation was performed in 33 (94%) infants and was abnormal in one infant who had chorioretinitis. All infants had newborn hearing screen performed and when abnormal, subsequent diagnostic testing showed sensorineural hearing loss in 21% (7/34) of infants with the majority of the hearing loss unilateral (4/7, 57%) and moderate-to-severe in severity (6/7, 86%). Five of the seven infants with hearing loss had neuroimaging abnormalities.

Antiviral therapy consisting of ganciclovir ($n = 2$), valganciclovir ($n = 12$), or both ($n = 4$) was provided to 53% (18/34) of infants (Table 4). The associated abnormalities that prompted antiviral therapy are provided in Table 4, although three infants in Buenos Aires who had normal evaluations received valganciclovir treatment based on detection of CMV by PCR in amniotic fluid.

Table 2 Results of laboratory, radiographic, ophthalmologic, and audiology evaluation in 34 infants with congenital CMV infection and a normal physical examination at birth

	Dallas	Buenos Aires	Total
No. of infants	14 (41%)	20 (59%)	34
No. of infants with at least 1 abnormality	7 (50%)	12 (60%)	19 (56%)
Laboratory evaluation	10 (71%)	15 (75%)	25 (71%)
Any abnormality	4 (40%)	11 (73%)	15 (60%)
Complete blood cell count	10 (40%)	15 (60%)	25 (100%)
Anemia (hematocrit; mean, range)	0	3 (20%) (35%, 30–39%)	3 (12%) (35%, 30–39%)
Thrombocytopenia (#/ml; mean, range)	2 (20%) (33,500; 10,000–57,000)	2 (13%) (126,000; 114,000–132,000)	4 (16%) (78,250; 10,000–132,000)
Hepatic assessment	8 (57%)	15 (75%)	23 (92%)
Elevated alanine aminotransferase (U/mL; mean, range)	2 (22%) (44.5, 43–46)	7 (78%) (55.5, 41–74)	9 (39%) (53, 41–74)
Direct hyperbilirubinemia	0	0	0
Neuroimaging	14 (100%)	10 (50%)	24 (71%)
Any abnormality	6 (43%)	5 (57%)	11 (46%)
Cranial ultrasonography	13 (93%)	9 (90%)	22 (92%)
Any abnormality	6 (46%)	4 (44%)	10 (45%)
Diffuse calcifications	1 (8%)	0	1 (55%)
Lenticulostriate vasculopathy	2 (14%)	3 (30%)	5 (23%)
Ventriculomegaly	1 (8%)	0	1 (5%)
Any Grade of IVH	5 (39%)	1 (11%)	6 (27%)
Grade I IVH	5 (100%)	0	5 (83%)
Grade II–III IVH ^a	0	1 (100%)	1 (17%)
Cranial computerized tomography	1 (7%)	1 (10%)	2/24 (8%)
Thalamic calcifications	0	1 (100%)	1 (50%)
Brain magnetic resonance imaging	2 (14%)	5 (50%)	7/24 (29%)
Periventricular calcifications and temporal lobe hyperlucency	0	1 (20%)	1 (14%)
Calcifications of thalami	0	1 (20%)	1 (14%)
Germinal matrix hemorrhage	1 (50%)	0	1 (14%)
Ophthalmologic evaluation	13 (93%)	20 (100%)	33 (97%)
Chorioretinitis	0	1 (5%)	1 (3%)
Audiologic evaluation (brainstem evoked responses)	14 (100%)	20 (100%)	34 (100%)
Sensorineural hearing loss	6 (43%)	1 (5%)	7 (21%)
Unilateral	3 (50%)	1 (100%)	4 (57%)
Bilateral	3 (50%)	0	3 (43%)
Mild	1 (17%)	0	1 (14%)
Moderate	2 (33%)	0	2 (29%)
Severe-profound	3 (50%)	1 (100%)	4 (57%)

^aNeonate born at 27 weeks' gestation

Discussion

The optimal evaluation of the well-appearing neonate with congenital CMV infection is not known, and beyond hearing screening and possibly ophthalmologic

examination, no recommendations exist [16]. This study sought to determine how frequently these “asymptomatic” infants have laboratory, ophthalmologic, and neuroimaging abnormalities that may predict risk for hearing loss and developmental delay. We found that as many as 56% of

Table 3 Results of neuroimaging studies in the four CMV-infected neonates who had more than one study performed

No. of patient	Site	Gestational age (week)	Weight (gram)	Sex	Cranial ultrasonography	Cranial computerized tomography	Brain magnetic resonance imaging
1	Dallas	37	2464	F	IVH grade I	Not done	Germinal matrix hemorrhage
2	Buenos Aires	38	2950	M	Lenticulostriate vasculopathy	Not done	Thalamic calcifications
3	Buenos Aires	34	1760	M	Lenticulostriate vasculopathy	Thalamic calcifications	Not done
4	Buenos Aires	38	3310	M	Normal	Not done	Periventricular calcifications and temporal lobe hyperlucency

IVH intraventricular hemorrhage

Table 4 Neonates with clinically inapparent congenital CMV infection who received antiviral therapy

No. of patient	Site	Gestational age (week)	Weight (gram)	Sex	Abnormality	Therapy, duration
1	Dallas	37	2770	M	Lenticulostriate vasculopathy, elevated ALT	Ganciclovir, 6 weeks
2	Dallas	29	860	M	Thrombocytopenia, ventriculomegaly, diffuse cerebral calcifications, IVH grade I	Ganciclovir, 6 weeks
3	Dallas	41	3295	M	Elevated ALT, IVH grade I, hearing loss	Valganciclovir, 6 weeks
4	Dallas	37	2464	F	IVH grade I, hearing loss	Valganciclovir, 6 weeks
5	Buenos Aires	34	1910	F	Anemia and thrombocytopenia	Ganciclovir, 14 days Valganciclovir, 6 months
6	Buenos Aires	40	3150	F	None	Valganciclovir, 6 months
7	Buenos Aires	40	3977	F	None	Valganciclovir, 6 months
8	Buenos Aires	40	3475	F	None	Valganciclovir, 6 months
9	Buenos Aires	38	2950	M	Anemia, lenticulostriate vasculopathy, thalamic calcifications	Valganciclovir, 6 months
10	Buenos Aires	40	3300	M	Thrombocytopenia	Valganciclovir, 6 months
11	Buenos Aires	38	2820	M	Elevated ALT	Valganciclovir, 6 months
12	Buenos Aires	30	1500	M	Lenticulostriate vasculopathy	Ganciclovir, 14 days Valganciclovir, 6 months
13	Buenos Aires	34	1760	M	Elevated ALT, lenticulostriate vasculopathy, thalamic calcifications	Ganciclovir, 14 days Valganciclovir, 6 months
14	Buenos Aires	38	3400	M	Elevated ALT	Valganciclovir, 6 months
15	Buenos Aires	38	2865	M	Elevated ALT	Valganciclovir, 6 months
16	Buenos Aires	38	2530	M	Elevated ALT	Valganciclovir, 6 months
17	Buenos Aires	38	3310	M	Elevated ALT, periventricular calcifications and temporal lobe hyperechogenicity	Valganciclovir, 6 months
18	Buenos Aires	27	1216	M	Anemia, IVH grade II–III, hearing loss	Ganciclovir, 14 days Valganciclovir, 6 months

ALT alanine aminotransferase, *IVH* intraventricular hemorrhage

neonates with congenital CMV infection and a normal physical examination had abnormalities that would reclassify them as “symptomatic.”

Among the laboratory tests performed, the most frequent finding was a mildly elevated serum ALT concentration even though no infant had signs of hepatitis including

hepatomegaly. Only one infant had chorioretinitis, although the importance of such a finding and its response to antiviral therapy likely makes ophthalmologic evaluation warranted in all neonates with congenital CMV infection [17–19].

Cranial ultrasound detected abnormalities in 45% of infants in whom the test was performed. Although

lenticulostriate vasculopathy is a nonspecific finding associated with a variety of conditions, it has been associated with congenital CMV infection and sensorineural hearing loss [20–24]. Grade 1 intraventricular hemorrhage also was a frequent finding, although its significance and possible relationship to congenital CMV infection remains unknown. Only four infants who had more than one neuroimaging test performed had abnormalities on at least one of them (Table 3). Cranial computerized tomography was abnormal in one of two infants, in which it was performed, and it demonstrated thalamic calcifications when the cranial ultrasound showed lenticulostriate vasculopathy (Table 3, patient #3). Similarly, MRI showed thalamic calcifications on one infant whose cranial ultrasound demonstrated lenticulostriate vasculopathy (Table 3, patient #3), while in a second infant (Table 3, patient #2), it showed periventricular calcifications and temporal lobe hyperlucency even though the ultrasound was normal.

Sensorineural hearing loss occurred in 21% of evaluated patients, higher than the 5–10% that has been reported previously among asymptomatic infants [25]. This likely represented selection bias as targeted CMV screening for referred hearing screen was performed during the study period. The fact that the hearing loss was moderate to severe in six (86%) infants and bilateral in three (43%) infants highlights the importance of targeted CMV screening of infants who refer on the newborn hearing screen [11, 26–28]. Unfortunately, this study did not include data on late-onset hearing loss which can occur in an additional 15–25% of CMV-infected infants [7].

The results of this study argue for a more complete evaluation of well-appearing neonates with congenital CMV infection. Using the disease classification of Rawlinson et al. [16], further evaluation of the study infants who had a normal physical examination and growth parameters classified seven infants with moderate-severe infection, ten with mild symptomatic infection, three with asymptomatic infection and isolated sensorineural hearing loss, and fourteen infants with asymptomatic infection. As universal screening for congenital CMV infection is being discussed and anticipated in the near future [29, 30], the need for such evaluation needs to be assessed and included as part of potential health benefits and cost analyses [31]. From this study, the performance of a complete evaluation (Table 5) may lead to institution of antiviral therapy to improve hearing and possibly neurodevelopmental outcomes in some infants [32–34].

Limitations of this study include the small sample size and its retrospective nature, and thus not all infants received comprehensive and consistent laboratory and radiological evaluation to know the actual incidence of specific abnormalities. Since the study included infants born since 1996, there may be a time bias with respect to management

Table 5 Evaluation of clinically “asymptomatic” neonates with congenital cytomegalovirus (CMV) infection who have a normal physical examination and growth parameters

- (1) Complete blood cell and platelet counts
- (2) Serum alanine aminotransferase (ALT) concentration
- (3) Serum total and direct bilirubin concentration
- (4) Serum creatinine concentration (if antiviral therapy initiated)
- (5) Blood quantitative CMV viral load
- (6) Cranial ultrasound^a
- (7) Ophthalmologic evaluation
- (8) Audiologic evaluation^b

^aMagnetic resonance imaging if further brain evaluation desired

^bNewborn hearing screen, and if not passed, then diagnostic auditory brainstem evoked responses

of these infants, as antiviral therapy has become more accepted with convenient oral administration. The latter may be a likely reason for the valganciclovir treatment of three infants in Buenos Aires who had a normal evaluation. In addition, 62% of the mothers in this convenience sample of CMV-infected infants were diagnosed with CMV during the pregnancy, and therefore the infants may have been more likely to have abnormalities than if they had been born to mothers with CMV reactivation. Nevertheless, 90% of these infants would have been expected to be “asymptomatic” as their physical examination and growth parameters suggested. Regardless, abnormalities detected on evaluation were not infrequent, suggesting that optimal classification of CMV-infected neonates to predict risk of sensorineural hearing loss will require such testing. In addition, infants did not have blood CMV DNA PCR testing that may help predict hearing outcomes [35]. Finally, the lack of an uninfected control group of infants may have resulted in an overestimate of the abnormalities attributable to congenital CMV infection, especially among the five preterm infants whose abnormal findings could have been related to prematurity. However, none of the term infants were diagnosed with other conditions that could have explained the abnormalities noted on laboratory, ophthalmologic, and neuroimaging evaluation.

In conclusion, well-appearing neonates with congenital CMV infection and a normal physical examination frequently have laboratory or neuroimaging abnormalities. This finding argues for performance of a more complete evaluation on these “asymptomatic” infants as suggested in Table 5 since some may benefit from antiviral treatment. Finally, these findings have important public health implications if universal CMV screening is adopted as standard care.

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Author contributions AR, had full access to all study data and is responsible for the data integrity and accuracy of the data analysis. He participated in the study concept and design, acquisition of data, analysis and interpretation of data, initial and subsequent drafts of the paper, and approved the final paper as submitted. FZ, participated in the study concept and design, acquisition of data, critical revision of the paper, and approved the final paper as submitted. L.E.L., participated in the study concept and design, acquisition of data, critical revision of the paper, and approved the final paper as submitted. K.E.O., participated in the study design, acquisition of data, critical revision of the paper, and approved the final paper as submitted. A.G.S., participated in the study concept and design, acquisition of data, critical revision of the paper, and approved the final paper as submitted. F.G., had full access to all study data and is responsible for the data integrity and accuracy of the data analysis. She participated in the study concept and design, acquisition of data, analysis and interpretation of data, initial and subsequent drafts of the paper, and approved the final paper as submitted. L.N.V., had full access to all study data and is responsible for the data integrity and accuracy of the data analysis. She participated in the study concept and design, acquisition of data, analysis and interpretation of data, initial and subsequent drafts of the paper, and approved the final paper as submitted. J.B.C., had full access to all study data and is responsible for the data integrity and accuracy of the data analysis. He participated in the study concept and design, acquisition of data, analysis and interpretation of data, initial and subsequent drafts of the paper, and approved the final paper as submitted. S.V., participated in the acquisition of data, critical revision of the paper, and approved the final paper as submitted. L.P., supervised the overall study by analysis and interpretation of data, critical revision of the paper for important intellectual content, and approved the final paper as submitted. P.J.S., had full access to all study data and is responsible for the data integrity and accuracy of the data analysis. He supervised the overall study by developing the study concept and design, acquisition of data, analysis and interpretation of data, initial and subsequent drafts of the paper, and approved the final paper as submitted.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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References

- Manicklal S, Emery VC, Lazzarotto T, Boppana SB, Gupta RK. The "silent" global burden of congenital cytomegalovirus. *Clin Microbiol Rev.* 2013;26:86–102.
- 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;17:355–63.
- Boppana SB, Ross SA, Shimamura M, Palmer AL, Ahmed A, Michaels MG, et al. Saliva polymerase-chain-reaction assay for cytomegalovirus screening in newborns. *New Engl J Med.* 2011;364:2111–8.
- Foulon I, Naessens A, Foulon W, Casteels A, Gordts F. A 10-year prospective study of sensorineural hearing loss in children with congenital cytomegalovirus infection. *J Pediatr.* 2008; 153:84–88.
- Madden C, Wiley S, Schleiss M, Benton C, Meinzen-Derr J, Greinwald J, et al. Audiometric, clinical and educational outcomes in a pediatric symptomatic congenital cytomegalovirus (CMV) population with sensorineural hearing loss. *Int J Pediatr Otorhinolaryngol.* 2005;69:1191–8.
- Cantey JB, Sanchez PJ. Overview of congenital infections: the prominence of cytomegalovirus. *Infect Disord Drug Targets.* 2011;11:426–31.
- Fowler KB. Congenital cytomegalovirus infection: audiologic outcome. *Clin Infect Dis.* 2013;57:S182–4.
- Rivera LB, Boppana SB, Fowler KB, Britt WJ, Stagno S, Pass RF. Predictors of hearing loss in children with symptomatic congenital cytomegalovirus infection. *Pediatrics.* 2002;110:762–7.
- Ross SA, Ahmed A, Palmer AL, Michaels MG, Sanchez PJ, Bernstein DI, et al. Detection of congenital cytomegalovirus infection by real-time polymerase chain reaction analysis of saliva or urine specimens. *J Infect Dis.* 2014;210:1415–8.
- Boppana SB, Ross SA, Novak Z, Shimamura M, Tolan RW Jr, Palmer AL, et al. Dried blood spot real-time polymerase chain reaction assays to screen newborns for congenital cytomegalovirus infection. *JAMA.* 2010;303:1375–82.
- Stehel EK, Shoup AG, Owen KE, Jackson GL, Sendelbach DM, Boney LF, et al. Newborn hearing screening and detection of congenital cytomegalovirus infection. *Pediatrics.* 2008; 121:970–5.
- Duryea EL, Sanchez PJ, Sheffield JS, Jackson GL, Wendel GD, McElwee BS, et al. Maternal human immunodeficiency virus infection and congenital transmission of cytomegalovirus. *Pediatr Infect Dis J.* 2010;29:915–8.
- Ellington SR, Clarke KE, Kourtis AP. Cytomegalovirus Infection in Human Immunodeficiency Virus (HIV)-Exposed and HIV-Infected Infants: a systematic review. *J Infect Dis.* 2016;213:891–900.
- Jopling J, Henry E, Wiedmeier SE, Christensen RD. Reference ranges for hematocrit and blood hemoglobin concentration during the neonatal period: data from a multihospital health care system. *Pediatrics.* 2009;123:e333–7.
- Northern JL, Downs MP. Hearing in children. USA: Lippincott Williams & Wilkins; 2001.
- Rawlinson WD, Boppana SB, Fowler KB, Kimberlin DW, Lazzarotto T, Alain S, et al. Congenital cytomegalovirus infection in pregnancy and the neonate: consensus recommendations for prevention, diagnosis, and therapy. *Lancet Infect Dis.* 2017;17: e177–88.
- Shoji K, Ito N, Ito Y, Inoue N, Adachi S, Fujimaru T, et al. Is a 6-week course of ganciclovir therapy effective for chorioretinitis in infants with congenital cytomegalovirus infection? *J Pediatr.* 2010;157:331–3.
- Coors LE, Spencer R. Delayed presentation of cytomegalovirus retinitis in an infant with severe congenital cytomegalovirus infection. *Retina.* 2010;30:S59–62.
- Ghekiere S, Allegaert K, Cossey V, Van Ranst M, Cassiman C, Casteels I. Ophthalmological findings in congenital cytomegalovirus infection: when to screen, when to treat? *J Pediatr Ophthalmol Strabismus.* 2012;49:274–82.
- Cantey JB, Sisman J. The etiology of lenticulostriate vasculopathy and the role of congenital infections. *Early Hum Dev.* 2015;91:427–30.

21. El Ayoubi M, de Bethmann O, Monset-Couchard M. Lenticulostriate echogenic vessels: clinical and sonographic study of 70 neonatal cases. *Pediatr Radiol*. 2003;33:697–703.
22. Bilavsky E, Schwarz M, Pardo J, Attias J, Levy I, Haimi-Cohen Y, et al. Lenticulostriated vasculopathy is a high-risk marker for hearing loss in congenital cytomegalovirus infections. *Acta Paediatr*. 2015;104:e388–94.
23. Amir J, Atias J, Linder N, Pardo J. Follow-up of infants with congenital cytomegalovirus and normal fetal imaging. *Arch Dis Child Fetal Neonatal Ed*. 2016;101:F428–32.
24. Amir J, Schwarz M, Levy I, Haimi-Cohen Y, Pardo J. Is lenticulostriated vasculopathy a sign of central nervous system insult in infants with congenital CMV infection? *Arch Dis Child*. 2011;96:846–50.
25. Goderis J, De Leenheer E, Smets K, Van Hoecke H, Keymeulen A, Dhooge I. Hearing loss and congenital CMV infection: a systematic review. *Pediatrics*. 2014;134:972–82.
26. Bergevin A, Zick CD, McVicar SB, Park AH. Cost-benefit analysis of targeted hearing directed early testing for congenital cytomegalovirus infection. *Int J Pediatr Otorhinolaryngol*. 2015;79:2090–3.
27. Fowler KB, McCollister FP, Sabo DL, Shoup AG, Owen KE, Woodruff JL, et al. A targeted approach for congenital cytomegalovirus screening within newborn hearing screening. *Pediatrics*. 2017;139:e20162128.
28. Diener ML, Zick CD, McVicar SB, Boettger J, Park AH. Outcomes from a hearing-targeted cytomegalovirus screening program. *Pediatrics*. 2017;139:e20160789.
29. 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;24:291–307.
30. Ronchi A, Shimamura M, Malhotra PS, Sanchez PJ. Encouraging postnatal cytomegalovirus (CMV) screening: the time is NOW for universal screening! *Expert Rev Anti Infective Ther*. 2017;15:417–9.
31. Gantt S, Dionne F, Kozak FK, Goshen O, Goldfarb DM, Park AH, et al. Cost-effectiveness of universal and targeted newborn screening for congenital cytomegalovirus infection. *JAMA Pediatr*. 2016;107:906.
32. Kimberlin DW, Jester PM, Sanchez PJ, Ahmed A, Arav-Boger R, Michaels MG, et al. Valganciclovir for symptomatic congenital cytomegalovirus disease. *New Engl J Med*. 2015;372:933–43.
33. Oliver SE, Cloud GA, Sanchez PJ, Demmler GJ, Dankner W, Shelton M, et al. Neurodevelopmental outcomes following ganciclovir therapy in symptomatic congenital cytomegalovirus infections involving the central nervous system. *J Clin Virol*. 2009;46:S22–6.
34. Kimberlin DW, Lin CY, Sanchez PJ, Demmler GJ, Dankner W, Shelton M, et al. Effect of ganciclovir therapy on hearing in symptomatic congenital cytomegalovirus disease involving the central nervous system: a randomized, controlled trial. *J Pediatr*. 2003;143:16–25.
35. Forner G, Abate D, Mengoli C, Palu G, Gussetti N. High cytomegalovirus (CMV) DNAemia predicts CMV sequelae in asymptomatic congenitally infected newborns born to women with primary infection during pregnancy. *J Infect Dis*. 2015;212:67–71.