Chapter 7
Cytomegalovirus & Hearing Impairment

N. Wendell Todd, MD, MPH; & Faye P. McCollister, EdD

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Cytomegalovirus (CMV) is an infectious disease that threatens hearing. CMV is the most frequently occurring congenital viral infection in babies in the United States (Oliver et al., 2009) and is now the leading cause of non-genetic hearing loss in babies. It has been reported that this virus causes approximately one-third of all pediatric hearing loss (Morton & Nance, 2006; Dahle et al., 2000). This infection is a member of the herpes virus family and most often causes no problems except when it occurs during pregnancy or in an immunocompromised individual (Fowler et al., 1992). Approximately 50 to 80% of adults are positive for the infection, and most are not aware that they carry it.

When the infection occurs during pregnancy, the symptoms for the host are often not detected, but it has the potential to cross the placenta and cause serious problems for the fetus. The congenital infection has no obvious symptomatology in newborns. For over 90% of the babies infected, that makes them difficult to identify without newborn CMV screening. Service providers for young children with this virus and with hearing loss often report it is not considered a public health problem, because they think it occurs very infrequently. Statements such as, "I have never seen a case of congenital CMV infection in all my years of practice," are not uncommon (for additional facts about CMV, see *Table 1*).

The only approved "on-label" treatment (intravenous ganciclovir) is for immunocompromised adult patients with CMV. In 2012, treatment of children with CMV is either in an institutional review board-approved research study or "off-label." Candidly, it must be stated that currently available treatment does not restore hearing but rather may prevent worsening of hearing (i.e., stabilizes auditory thresholds).

Developmental Considerations

The developmental problems that result from the congenital infection are more likely to occur when it is a primary infection—during the first 26 weeks of gestation (Fowler & Bopanna, 2006). Of CVM-positive babies, 10% have identifiable

NCHAM National Center for Hearing Assessment and Management Utah State University™

Table 1
Facts about CMV

Quick Facts about CMV

- Though there are numerous strains of CMV (Renzette et al., 2011), only human strains of the virus are known to produce human disease.
- Most CMV infections are "silent;" that is, most infected people have no symptom or sign of having CMV.
- Though CMV are everywhere among us, 30-50% of women of childbearing age in the United States have not been infected with CMV.
- Of the 1-4% of women who get infected with CMV during pregnancy, about one-third pass the virus to the baby.
- 1 of 100 newborns in United States has congenital CMV, but 90% of these appear healthy at birth and pass newborn auditory physiologic screening.
- Overall, about 1 of 1,000 newborns in the United States is identified to have congenital CMV.
- Vertical transmission of CMV from mother to infant happens in three ways and times: (1) in utero transplacental, (2) vaginal delivery through CMV-infected secretions, (3) ingestion of CMV-infected human milk.
- Horizontal transmission of CMV occurs by direct person-to-person contact with CMV-containing body fluids (e.g., saliva, urine).
- 80% of congenitally infected babies never develop any symptom or disability attributable to CMV.
- CMV establishes lifelong latency and is not eliminated from the body with 2012 antiviral treatment of CMV disease.
- Since babies with congenital CMV infection are not screened for the virus, and since many of these children have delayed onset hearing loss, they will pass newborn hearing screening and be missed for asymptomatic CMV in any risk factor screening protocol. This group of children contributes substantially to the large unknown etiology category evident in most studies of etiology of pediatric hearing loss (Fowler, Dahle, Bopanna, & Pass, 1999).

Diagnosis of CMV

- Strong evidence that the disease is caused by CMV infection exists when the virus is recovered from a target organ, e.g. liver.
- Detecting virus excretion in urine, stool, respiratory tract secretions (including saliva), or cerebrospinal fluid can make a *presumptive diagnosis* of congenital CMV.
- The distinction of congenital versus acquired CMV infection cannot be made unless virus is detected within the first 3 weeks of life—in which situation, the infection is considered congenital.
- A *presumptive diagnosis* of CMV can be made on the basis of a four-fold IgM antibody titer increase.

The certainty of CMV diagnosis is befuddled by the following . . .

1. High rate of asymptomatic virus excretion by babies.
2. High rate of reactivation of infections.
3. Development of serum immunoglobulin (IgM CMV-specific antibody) in some episodes of reactivation.
4. Reinfections with different strains of CMV.
5. Concurrent infection with other pathogens.

problems, including jaundice, microcephaly, intrauterine growth retardation, hepatospleenomegaly, thrombocytopenia, petechiae, and periventricular calcifications. The 90% of CMV-positive babies who are asymptomatic are usually not identified but may have hearing problems, vision problems, and/or seizure disorders (Fowler et al., 1997). Hearing impairment is the most frequent problem in "asymptomatic CMV-positive" babies.

Longitudinal Study of Hearing

The most comprehensive longitudinal study of hearing was reported by Dahle and colleagues in 2000. This report describes the variety of hearing loss that occurs in symptomatic and asymptomatic subjects. The primary findings to date indicate hearing loss may be present at birth or may occur much later in a child's life. Progression of the hearing loss occurs frequently and may occur early after birth or several years later. Fluctuations in hearing are evident in hearing loss associated with symptomatic and asymptomatic infections. The hearing loss can be bilateral or unilateral and has no characteristic configuration; cases with high frequency loss, flat configuration, and reverse slope configurations have been reported. Subjects who are at high risk of having hearing sequelae are those with "symptomatic infection." Those with "asymptomatic infection," except for the hearing problem, comprise the largest percentage of the population impacted and therefore have the greatest public health influence simply by the number of children affected.

Research

Research is currently being conducted, including the CHIMES Study at the University of Alabama at Birmingham. CHIMES is a multisite investigation designed to evaluate CMV newborn screening methodologies and to characterize hearing loss. This study is funded by the National Institute on Deafness and Communication Disorders (NIDCD) and directed by Dr. Suresh Bopanna and Dr. Karen Fowler. Data has demonstrated that the saliva polymerase-chain-reactive assay protocol is efficient in identifying congenital CMV infection when conducted during the first 3 weeks of life. The dried blood spot test was shown to have decreased sensitivity and specificity (Bopanna et al., 2011). This study has collected longitudinal audiological information from seven pediatric hospitals across the country and should provide additional information on characteristics of hearing loss associated with congenital CMV infection.

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Clinical Presentation

Practitioners providing hearing services to young children rarely have the advantage of knowing if the child they are seeing has congenital CMV infection. When etiology is not known and cannot be established, management protocols should address the fact that CMV is a potential etiology. Strong evidence that CMV infection exists when the virus is recovered from a target organ, e.g. liver. Evidence for a *presumptive diagnosis* of congenital CMV is when CMV virus is found in the first 3 weeks of life in urine, stool, respiratory tract secretions (including saliva), or cerebrospinal fluid. Clinicians face many more children whose clinical scenario is consistent with CMV infection than the number of children with even a *presumptive diagnosis* of CMV (see *Table 2*).

Audiological Assessment

The Joint Committee on Infant Hearing (JCIH) recommendations specifically include CMV for more frequent assessments because of the documented high rates of delayed onset and progressive hearing loss (JCIH, 2007).

Table 2

Clinical Pictures of CMV Encountered by the Early Hearing Detection and Intervention (EHDI) Practitioner

Considerations	Clinical Pictures of CMV and Hearing Loss			
	Congenital CMV - symptomatic with or without sensorineural hearing loss	**Congenital CMV -** asymptomatic except sensorineural hearing loss	**Acquired CMV, immunocompetent -** symptomatic with [at least] sensorineural hearing loss	**Sensorineural Hearing Loss** explanation unknown
Method to diagnose CMV	Examination findings of newborn (e.g., intrauterine growth restriction, jaundice, purpura, hepatosplenomegaly, microcephaly, intracerebral calcifications, retinitis), plus virus found in target organ and/or body fluid	At age less than 3 weeks, CMV found in body fluid	Four-fold titer rise IgM to CMV	Circumstantial: passed or failed UNHS; progressive hearing loss, ear imaging normal; microcephaly, retinitis, or brain imaging consistent with CMV
Certainty of CMV diagnosis	Excellent	Probably good	Probably fair	Probably poor
Koch's postulates met	Yes	No	No	No
Likelihood of hearing worsening	At least 50%	About 50:50	Unknown	Unknown
Treatment	Though none are FDA-approved in 2012, many pediatricians would consider treating	None are FDA-approved in 2012	None are FDA-approved in 2012	None
What is the EHDI practitioner to do for the patient?	Monitor hearing, amplify—may eventually consider cochlear implant	Monitor hearing, amplify—may eventually consider cochlear implant	Monitor hearing, amplify—may eventually consider cochlear implant	Monitor hearing, amplify—may eventually consider cochlear implant
What is the EHDI practitioner to do for the science?	Encourage and participate in rigorous scientific studies about patients suffering CMV	Encourage and participate in rigorous scientific studies about patients suffering CMV	Encourage and participate in rigorous scientific studies about patients suffering CMV	Encourage evidence-based, long-term, comprehensive care—remembering the irreplaceable value of Temporal Bone Registry

Infection Control to Prevent Congenital CMV Infection

Table 3 lists a few simple steps you can take to avoid exposure to saliva and urine that might contain CMV.

Interdisciplinary Partners, Referrals, and Collaboration

Children with CMV, whether the evidence is strong, presumptive, or suspect-but-nonproven, are—as are all other children—best attended in the "medical home" in conjunction with a host of other professionals and collaborators. For further information on the "medical home," see the appropriate chapter in this publication.

Policy/Procedure Gaps

- Perhaps not-passing newborn auditory physiologic screening should be considered a sign that CMV infection may be present at birth, triggering urine assay for CMV.
- Perhaps not-passing newborn auditory physiologic screening also should be considered an indication for ophthalmologic consultation for retinal examination.
- Having not passed newborn hearing screening should be contemplated during the care of a baby with "failure to thrive."

Illustrative Cases of Diagnostic Pitfall Worsening Hearing

Table 3
Simple Steps to Avoid Exposure to CMV

(copied 2/1/2013 from http://www.cdc.gov/cmv/prevention.html)

Step 1

Wash your hands often with soap and water for 15-20 seconds, especially after:

- Changing diapers.
- Feeding a young child.
- Wiping a young child's nose or drool.
- Handling children's toys.

Step 2

Do not share food, drinks, or eating utensils used by young children.

Step 3

Do not put a child's pacifier in your mouth.

Step 4

Do not share a toothbrush with a young child.

Step 5

Avoid contact with saliva when kissing a child.

Step 6

Clean toys, countertops, and other surfaces that come into contact with children's urine or saliva.

Case 1

A 32-month-old boy came with his biologic grandmother, who identified herself as the legal guardian, because of concern for poor hearing. He was born at term, passed newborn hearing screening, and was considered normal until age 2 years when he was hit in the head by a golf ball. With no loss of consciousness, medical attention was not sought at the time. Examination at age 32-months was unremarkable except for visual hyper-attentiveness; normal tympanograms; otoacoustic emissions not found; auditory brainstem response study showed the only responses to be in one ear to tone bursts centered at 0.5 and 1kHz at 70 and 75dBnHL, respectively. MRI was reported as normal temporal bones, but patchy and confluent T2 hyper-intensity in periatrial white matter bilaterally. CMV was the suspected etiology. The next month, the geneticist reported, "long arm of chromosome 10 absent." The child utilizes "total communication."

Case 2

A girl came with her biologic grandparents, who identified themselves as legal guardians, at age 24 months because of degradation of her talking. The girl was delivered by C-section (the mother had suffered neurologic damage due to motor vehicle accident during the pregnancy, after which she developed positive titer to CMV) at 37 weeks gestation, weight 3.1kg. She was hospitalized at age 32 days, weight 3.4kg, for failure to thrive: situs inversus totalis; nasal brush biopsy was reported consistent with Kartagener syndrome. Normal head circumference. No heart disease. Gaining weight after formula change, she went home after four nights. CMV was found in urine specimen obtained at age 6 days. Ganciclovir was not prescribed.

That she had not passed newborn hearing screening was ignored until age 24 months: her verbal expressive language skills until about age 20 months were thought normal. Otitis prompted tympanostomy-tube placement at age 11 months. She began walking at age 22 months. ABR at age 25 months was consistent with severe hearing loss right ear, no response left ear. MRI at age 27 months showed normal temporal bones, but extensive polymicrogyria of left cerebral hemisphere and bilateral T2 hyper-intensity of white matter. Hearing aids, fitted at age 25 months, did not boost into the "speech banana." Cochlear implant left ear at age 33 months yielded, with help of auditory-verbal therapy, such positive benefit that contralateral implantation is planned. Ophthalmologic examinations done at ages 9 months through 32 months were persistently normal. Neither pulmonary nor nasal problem has manifested, so the immotile cilia diagnosis is suspect.

Would this child have fared better if her failing the newborn hearing screening had been contemplated during the workup of "failure to thrive?" Would she have fared better if diagnostic audiologic battery had been completed by age 3 months? If treated with ganciclovir in the first weeks?

Would this child have fared better if her failing the newborn hearing screening had been contemplated during the workup of "failure to thrive?"

Resources and Suggested Readings:

- Centers for Disease Control and Prevention (CDC) CMV Homepage, http://www.cdc.gov/cmv/index.html
- CDC Podcast on Congenital CMV, http://www2.cdc.gov/podcasts/player.asp?f=7925
- CDC 10 Tips for Preventing Infections during Pregnancy, http://www.cdc.gov/features/pregnancy/
- National Congenital CMV Disease Registry, http://www.bcm.edu/pedi/infect/cmv
- Stop CMV, http://www.stopcmv.com/
- Lisa Saunders—What you need to know about CMV, http://congenitalcmv.blogspot.com/
- Kids Health, http://kidshealth.org/parent/infections/bacterial_viral/cytomegalovirus.html
- CMVSupport (United Kingdom), http://www.cmvsupport.org/modules/news/

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