

# Congenital Cytomegalovirus Infection: Impairment and Immunization

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(See the articles by Ogawa et al., on pages 782–8, and by Schleiss et al., on pages 789–98.)

It has been 50 years since Smith [1] and Weller et al. [2] separately reported the isolation and propagation of a cytopathogenic virus from tissues of infants with cytomegalic inclusion disease. In the intervening half century, much has been learned about congenital cytomegalovirus (CMV) infection, as well as the epidemiological, transmission, and molecular biological characteristics of CMV and the natural history of CMV infection. Unfortunately, no means of preventing congenital CMV infection or its cognitive, motor, or sensory sequelae is available or even on the visible horizon. In this issue of the *Journal*, Ogawa et al. [3] and Schleiss et al. [4] add to our knowledge of the role of congenital CMV infection in severe hearing loss and inform continuing investigation of vaccine approaches to pre-

vention, respectively. The respective topics of these reports—hearing loss and vaccine prevention—also remind us that research on congenital CMV infection continues to be driven by the initiative of individual investigators.

Ogawa et al. [3] took advantage of umbilical-cord specimens, which are saved by families in Japan as a keepsake. They tested children with severe sensorineural hearing loss for congenital CMV infection and for the connexin 26 gene, *GJB2*, mutations in which are the leading genetic cause of hearing loss. Although knowledge about the sensitivity and specificity of the polymerase chain reaction (PCR) assay used for the detection of human CMV (HCMV) glycoprotein H and the real-time PCR assay for UL83 is not extensive, the authors report that umbilical-cord samples from 4 children with known congenital CMV infection were all positive when both assays were used and that samples from 17 healthy children were all negative. Among children with severe hearing loss, 10 (15%) were positive for CMV by both PCR assays, and 16 (24%) were positive for mutations in *GJB2*. There was no overlap in the 2 groups; none of the children with congenital CMV infection had mutations in the connexin 26 gene. This study provides evidence that congenital CMV infection and *GJB2* mutations account for roughly similar proportions of severe hearing loss in children in Japan and that

the association between congenital CMV infection and hearing loss is not due to the coincident occurrence of CMV infection in children with *GJB2* mutations. Review of the medical records of the children with congenital CMV infection showed that 3 had signs or symptoms that should have led to suspicion of congenital infection at birth and that 2 of them had laboratory confirmation of congenital CMV infection as newborns. However, the role of congenital CMV infection in the other 7 children would not have been known without Ogawa et al.'s study. Half of the children with congenital CMV developed hearing loss after 6 months of age and would not have been detected by newborn hearing screening programs. More than 90% of mothers in Japan are immune to CMV before pregnancy [5]. Because maternal immunity provides substantial protection against hearing loss with congenital CMV infection, one might expect the proportion of cases of severe hearing loss in children due to CMV to be higher in countries in which more women are susceptible to primary infection during pregnancy. In Sweden, the prevalence of maternal immunity to CMV is lower, at ~60%–70% [6]. A Swedish cohort study that screened 10,328 newborns for congenital CMV infection found a high proportion of cases of deafness to be due to congenital CMV infection (40%), with CMV and hereditary causes accounting

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for roughly similar proportions, although that study did not include DNA testing for gene mutations associated with hearing loss [7]. Although the importance of congenital CMV infection as a cause of hearing loss in children is well established, an approach to dealing with this problem is not part of the enormous public health effort directed at the early detection of hearing loss in infants. Detection of hearing loss due to CMV will not be achieved by universal newborn hearing screening, because in approximately one-half of infants with congenital CMV infection in whom hearing loss develops, it appears or progresses to a severe level after the neonatal period.

The rationale for screening newborns for hearing loss is that the early identification of hearing loss will allow interventions that lead to improved speech and language skills, reading ability, and academic performance. Although questions about the effectiveness of universal newborn hearing screening in achieving these goals remain, newborn screening has progressed from multiple large, government-sponsored studies of feasibility to a public health policy that is mandated by most states in the United States [8]. This policy has essentially ignored the role of congenital CMV infection. Although effective antiviral treatment of congenital CMV infection is not yet a reality, there is evidence that ganciclovir treatment of newborns improved the hearing outcome in those with severe symptomatic congenital CMV infection [9]. With improved approaches to antiviral treatment, it is possible that hearing loss could be prevented. Thus, the rationale for including CMV in newborn screening programs might initially be early intervention with rehabilitation, but, eventually, it will be antiviral treatment with the aim of preventing disability.

Development of a vaccine to prevent congenital CMV infection was identified as a top priority for vaccine research in the United States by a committee of the Institute of Medicine of the National Academy of Sciences in a report published

in 2001 [10]. A variety of approaches to CMV vaccines are now in preclinical or early clinical development. Because of the importance of cell-mediated immunity in controlling chronic viral infections, a CMV vaccine that includes key immunogens for stimulation of cytotoxic T lymphocyte responses and presents these immunogens through intracellular pathways in the context of HLA class I is desirable. Schleiss et al. [4] used a vaccine composed of the guinea pig CMV (GPCMV) tegument protein gene GP83 in a proprietary vector—a modified alphavirus that undergoes a single cycle of replication—to immunize guinea pigs before conception. They achieved a significant reduction in fetal loss after challenge late during gestation. The alphavirus-vectored GP83 was immunogenic, stimulating both antibody and cell-mediated immune responses, and immunized dams had lower levels of viremia after challenge than did controls. GP83 is the guinea pig homolog of the HCMV gene *UL83*, which encodes a 65-kDa phosphoprotein that is a major component of the viral tegument and is one of the most important viral proteins for stimulating cytotoxic T lymphocyte responses [11]. Although immunization with the GP83 vaccine was associated with a reduced rate of fetal infection, there was not a statistically significant difference in the rate of congenital infection in live-born pups of immunized dams, compared with that in controls. However, in previous studies, immunization with a lectin-purified GPCMV glycoprotein vaccine and with a DNA vaccine encoding GPCMV glycoprotein B (major target of neutralizing antibody) each significantly reduced the rate of transplacental transmission of GPCMV, as well as the rate of pup mortality [12, 13]. The evaluation of a GPCMV vaccine that includes both glycoprotein B and GP83 in the congenital CMV model seems to be a logical next step.

The fact that HCMV is species specific complicates the use of small animal models. The guinea pig is an attractive model

for preclinical testing of novel approaches to CMV vaccine because the guinea pig placenta is similar to that of humans, in that a single trophoblast layer separates maternal and fetal circulation and transplacental transmission of GPCMV occurs predictably under the appropriate experimental conditions. There are some obvious differences between maternal and fetal CMV infection in humans and the GPCMV congenital infection model. Parenteral routes of infection are usually used in the experimental animal to facilitate maternal infection, whereas human infection is probably transmitted more often by mucosal contact with infectious material from another person. Fetal loss is not a common consequence of CMV infection during human pregnancy, although it is the end point most consistently used in studies of congenital GPCMV. The impact of congenital CMV infection in humans is measured by central nervous system and sensory impairments. In addition, there are likely to be some significant differences in the biological characteristics of HCMV and GPCMV, although there appear to be important similarities. An approach to vaccination that prevents the transplacental transmission of GPCMV and then can be used with HCMV to prevent congenital CMV infection is the hoped-for ultimate validation of the guinea pig model.

Vaccine development and early detection of hearing loss are 2 areas in which the importance of focused, goal-oriented national programs has been demonstrated. Despite the continued excellent efforts of investigators, another 50 years could pass before we are able to prevent congenital CMV infection. What has been lacking in this field is for the federal research and public health authorities to make the goal of prevention of congenital CMV infection the national priority that it should be.

## References

1. Smith MG. Propagation in tissue cultures of a cytopathogenic virus from human salivary

- gland virus (SGV) disease. *Proc Soc Exp Biol Med* **1956**;92:418–24.
2. Weller TH, Macaulay JC, Craig JM, Wirth P. Isolation of intranuclear inclusion producing agents from infants with illnesses resembling cytomegalic inclusion disease. *Proc Soc Exp Biol Med* **1957**;94:4–12.
  3. Ogawa H, Suzutani T, Baba Y, et al. Etiology of severe sensorineural hearing loss in children: independent impact of congenital cytomegalovirus infection and *GJB2* mutations. *J Infect Dis* **2007**;195:782–8 (in this issue).
  4. Schleiss MR, Lacayo JC, Belkaid Y, et al. Preconceptual administration of an alphavirus replicon UL83 (pp65 homolog) vaccine induces humoral and cellular immunity and improves pregnancy outcome in the guinea pig model of congenital cytomegalovirus infection. *J Infect Dis* **2007**;195:789–98 (in this issue).
  5. Hirota K, Muraguchi K, Watabe N, et al. Prospective study on maternal, intrauterine, and perinatal infections with cytomegalovirus in Japan during 1976–1990. *J Med Virol* **1992**;37:303–6.
  6. Ahlfors K. IgG antibodies to cytomegalovirus in a normal urban Swedish population. *Scand J Infect Dis* **1984**;16:335–7.
  7. Harris S, Ahlfors K, Ivarsson S, Lemmark B, Svanberg L. Congenital cytomegalovirus infection and sensorineural hearing loss. *Ear Hear* **1984**;5:352–5.
  8. Thompson DC, McPhillips H, Davis R, Lieu TA, Homer CJ, Helfand M. Universal newborn hearing screening: summary of evidence. *JAMA* **2001**;286:2000–10.
  9. Kimberlin DW, Lin CY, Sanchez PJ, 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.
  10. Stratton K, Durch J, Lawrence R. Vaccines for the 21st century: a tool for decisionmaking. Washington, DC: National Academy Press, **2001**.
  11. McGregor A, Liu F, Schleiss MR. Molecular, biological and in vivo characterization of the guinea pig cytomegalovirus (GPCMV) homologs of the HCMV matrix proteins, pp71 (UL82) and pp65 (UL83). *J Virol* **2004**;78:9872–89.
  12. Bourne N, Schleiss MR, Bravo F, Bernstein DI. Preconception immunization with a cytomegalovirus (CMV) glycoprotein vaccine improves pregnancy outcome in a guinea pig model of congenital CMV infection. *J Infect Dis* **2001**;183:59–64.
  13. Schleiss MR, Bourne N, Bernstein DI. Preconception vaccination with a glycoprotein B (gB) DNA vaccine protects against cytomegalovirus (CMV) transmission in the guinea pig model of congenital CMV infection. *J Infect Dis* **2003**;188:1868–74.