

Natural history studies bring universal screening for congenital CMV infection closer

Slowly but surely we are moving towards a time when universal screening of all neonates to detect congenital cytomegalovirus (CMV) infection will be routine.

The reasons are well known. CMV is the commonest cause of congenital infection, damages the intellectual potential of as many babies as does Down syndrome and is the single most common cause of sensorineural hearing loss (SNHL) in children.(1-3) Performing tests for CMV in those who fail neonatal hearing screening identifies some cases of SNHL but misses the majority, because many CMV cases do not develop SNHL until later in life.(4, 5) Valganciclovir given within a month of birth to babies born with symptoms of congenital CMV infection reduces hearing loss, but this treatment cannot be considered in most cases of congenital infection because only a minority exhibit signs at birth.(6) Universal screening of all babies for congenital CMV infection is predicted to be cost-effective and even cost saving under some scenarios.(7)

Each jurisdiction responsible for considering whether a screening programme should be expanded to include another condition such as CMV has a series of criteria that must be met.(8) Congenital CMV infection meets most of these criteria already, but is distinctly different from other conditions that are currently screened for; it is far more common and most cases of CMV infection will not develop disease on follow-up. There is thus the concern that screening for congenital CMV might swamp audiology clinics with children whose hearing remains normal, thereby worrying parents unnecessarily. The sheer number of cases of congenital CMV might also interfere with provision of services needed for children whose hearing is impaired due to any cause which increase over the first few years of life.(3) This potential problem could be mitigated if we could identify at birth those children most at risk of developing disease caused by congenital CMV and two recent papers report important information to help achieve this.

The natural history of congenital CMV infection is complex. Mothers can experience primary infection, reactivation of latent CMV or reinfection with a new strain of CMV during pregnancy (the latter two pooled under the term recurrent infection). The addition of antibody avidity tests to those for CMV IgG and IgM antibodies has improved the ability to differentiate primary infection from recurrent infection caused by either reactivation or reinfection.(9, 10) Several years ago this journal published a review of the complex relationship between maternal seropositivity and the incidence of congenital infection in the same population.(11) Essentially, in all countries of the world, more babies with congenital CMV are born to women with recurrent infection than to women with primary infection.(11, 12)

Now, a paper from Brazil, a country with virtually 100% seroprevalence, reports a difference in the development of progressive SNHL.(13) A total of 11,900 babies were screened at birth for both SNHL and congenital CMV

infection. In total, 68 neonates had congenital CMV and 24 had confirmed SNHL. Overall, 7/24 (29%) of cases of SNHL in Brazil were attributable to CMV, a figure similar to that reported from other countries.(4) What was different from the published literature was that none of 49 babies in the study with congenital CMV who had normal hearing at birth developed SNHL when followed prospectively with serial hearing tests for a median of 36 months.(13) This means that, once universal screening is introduced, the parents of children born to mothers with recurrent infection could be reassured that close monitoring for hearing loss is not required if the protocol followed in Brazil had been followed. It should be noted that universal hearing screening programmes examine babies for otoacoustic emissions.(3, 4) Those that do not clearly pass this test proceed to be examined further using automated auditory brainstem responses. Neonates with a higher than average clinical risk of hearing loss, such as receipt of aminoglycosides, are given both tests. Most babies born with congenital CMV infection cannot be scheduled to receive both tests because they do not have symptoms. However, by testing all neonates for congenital CMV, the Brazilian investigators were able to categorise them as high risk and so get both hearing tests done.(13) This is one potential difference from other published studies.(4)

The second study comes from France and describes the careful definition of primary CMV infection at different stages of pregnancy.(14) A total of 255 women had proven primary CMV infection and their babies were followed for a median of 24 months with tests of hearing and neurological function. All of the severe CNS and/or SNHL disease was seen following infection in the first trimester (risk 32%) compared with zero disease in the second and third trimesters.(14) This means that, once universal screening is introduced, the needed resources for close monitoring could be focused on the subgroup with first trimester infections rather than those whose mothers had primary infection later in pregnancy.

The absence of symptoms in women with recurrent infection and the lack of laboratory tests able to localise recurrent infection to particular stages of pregnancy frustrates our ability to combine the results of these two studies in terms of pathogenesis. Nevertheless, it is tempting to speculate that CMV is most pathogenic when it infects the fetus in early pregnancy, irrespective of the type of maternal infection that led to intrauterine transmission.

The results from these two new important studies suggest that universal screening for congenital CMV could be implemented by testing the infected cases using the high risk protocol of both otoacoustic emissions plus automated auditory brainstem responses.(13) Thereafter, close monitoring could be offered only to those whose mothers had primary infection in the first trimester. All other children (the vast majority of cases) could have hearing tests appropriate for their age as part of routine provision for hearing screening in each country.(3) This would dramatically reduce the health care costs associated with following all babies born with congenital CMV infection provided that expert evaluation of stored sera collected during pregnancy could be performed, perhaps in regional reference laboratories, as described

by colleagues in Italy, to distinguish between primary and recurrent CMV.(9, 10)

This suggestion of not making special provision for most cases of congenital CMV may be criticised by some who want to see SNHL caused by CMV detected at the earliest possible time. However, without universal screening, these cases, and many of the high risk ones as well, will continue to be ignored by our current healthcare systems.(15) As we push for implementation of universal screening, we must be realistic enough to be prepared to accept the benefits of a good screening programme, even if it is not the perfect model previously imagined. Universal screening for congenital CMV would supplement the existing practice of examining babies for symptoms at birth and classify any with congenital infection as needing tests for hearing according to the high risk protocol. Close audiological follow up could then be focused only on cases infected following primary maternal infection in the first trimester. This strategy could be audited to determine how many cases of very late onset disease are actually missed in practice.

PD Griffiths

1. Dollard SC, Grosse SD, Ross DS. New estimates of the prevalence of neurological and sensory sequelae and mortality associated with congenital cytomegalovirus infection. *RevMed Virol.* 2007;17(5):355-63.
2. Cannon MJ, Davis KF. Washing our hands of the congenital cytomegalovirus disease epidemic. *BMCPublic Health.* 2005;5:70.
3. Morton CC, Nance WE. Newborn hearing screening--a silent revolution. *The New England journal of medicine.* 2006;354(20):2151-64.
4. 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 Feb;139(2). PubMed PMID: 28049114. Pubmed Central PMCID: 5260148 conflicts of interest to disclose.
5. Dahle AJ, Fowler KB, Wright JD, Boppana SB, Britt WJ, Pass RF. Longitudinal investigation of hearing disorders in children with congenital cytomegalovirus. *JAmAcadAudiol.* 2000;11(5):283-90.
6. Kimberlin DW, Jester PM, Sanchez PJ, Ahmed A, Arav-Boger R, Michaels MG, et al. Valganciclovir for symptomatic congenital cytomegalovirus disease. *The New England journal of medicine.* 2015 Mar 5;372(10):933-43. PubMed PMID: 25738669. Pubmed Central PMCID: 4401811.
7. 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 Dec 1;170(12):1173-80. PubMed PMID: WOS:000390256900017. English.
8. Grosse SD, Dollard S, Ross DS, Cannon M. Newborn screening for congenital cytomegalovirus: Options for hospital-based and public health

programs. *Journal of Clinical Virology*. 2009 Dec;46:S32-S6. PubMed PMID: WOS:000273109500007. English.

9. Revello MG, Fabbri E, Furione M, Zavattoni M, Lilleri D, Tassis B, et al. Role of prenatal diagnosis and counseling in the management of 735 pregnancies complicated by primary human cytomegalovirus infection: a 20-year experience. *JClinViro*. 2011;50(4):303-7.

10. Guerra B, Simonazzi G, Banfi A, Lazzarotto T, Farina A, Lanari M, et al. Impact of diagnostic and confirmatory tests and prenatal counseling on the rate of pregnancy termination among women with positive cytomegalovirus immunoglobulin M antibody titers. *AmJObstetGynecol*. 2007;196(3):221-6.

11. de Vries JJ, van Zwet EW, Dekker FW, Kroes AC, Verkerk PH, Vossen AC. The apparent paradox of maternal seropositivity as a risk factor for congenital cytomegalovirus infection: a population-based prediction model. *RevMedViro*. 2013;23(4):241-9.

12. Zuhair M, Smit GSA, Wallis G, Jabbar F, Smith C, Devleesschauwer B, et al. Estimation of the worldwide seroprevalence of cytomegalovirus: A systematic review and meta-analysis. *Reviews in medical virology*. 2019 May;29(3):e2034. PubMed PMID: 30706584.

13. Yamamoto AY, Anastasio ART, Massuda ET, Isaac ML, Manfredi AKS, Cavalcante JMS, et al. Contribution of congenital cytomegalovirus (cCMV) to permanent hearing loss in a highly seropositive population: "The BraCHS study". *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 2019 May 17. PubMed PMID: 31102409.

14. Faure-Bardon V, Magny JF, Parodi M, Couderc S, Garcia P, Maillotte AM, et al. Sequelae of congenital cytomegalovirus (cCMV) following maternal primary infection are limited to those acquired in the first trimester of pregnancy. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 2018 Dec 31. PubMed PMID: 30596974.

15. Cannon MJ, Griffiths PD, Aston V, Rawlinson WD. Universal newborn screening for congenital CMV infection: what is the evidence of potential benefit? *Reviews in medical virology*. 2014 Sep;24(5):291-307. PubMed PMID: WOS:000344544900002. English.