Congenital cytomegalovirus infection in Canada: Active surveillance for cases diagnosed by paediatricians

Wendy Vaudry MD CM[1], Bonita E Lee MD MSc[1], Rhonda J Rosychuk PhD[1,2]

W Vaudry, BE Lee, RJ Rosychuk. Congenital cytomegalovirus infection in Canada: Active surveillance for cases diagnosed by paediatricians. Paediatr Child Health 2014;19(1):e1-e5.

OBJECTIVE: To determine the rate of diagnosis; demographic, clinical and laboratory characteristics; and management of congenital cytomegalovirus (cCMV) cases identified by paediatricians in routine clinical practice in Canada.

METHODS: National active monthly surveillance of all clinically practicing general and subspecialty paediatricians in Canada was performed for cCMV from March 1, 2005 to February 28, 2008, through the Canadian Paediatric Surveillance Program.

RESULTS: Forty-nine cases of cCMV infection were reported (4.5 per 100,000 births): 40.8% were born before 36 weeks' gestation; 55.1% had a birth weight <2500 g; and 28.6% and 30.6% were below the third percentile for weight and head circumference, respectively. The median maternal age was 23 years, and 18.4% were <20 years of age. Eight mothers (16.3%) were Aboriginal (non-Aboriginal birth prevalence 3.9 per 100,000; Aboriginal birth prevalence 15.8 per 100,000; P<0.005). The most common laboratory abnormality was thrombocytopenia (53.1%). Thirty-three (67.3%) infants exhibited neurological manifestations; ganciclovir therapy was administered to 12 (36.4%) and was not administered to 21 (63.6%) of the infants with neurological manifestations.

CONCLUSION: Only a minority of the expected number of symptomatic cCMV-infected infants were reported in the present study. The majority of these severely affected infants, including those with neurological disease, are not being treated with ganciclovir. The present description of current diagnosis and practice highlights the need for more complete case identification in the population as well as the need for increased awareness of the optimal therapy for symptomatic cCMV.

Key Words: *Aboriginal; Canada; Congenital infection; Cytomegalovirus; Surveillance*

L'infection à cytomégalovirus congénitale au Canada : la surveillance active des cas diagnostiqués par des pédiatres

OBJECTIF : Déterminer le taux de diagnostics, les caractéristiques démographiques, cliniques et de laboratoire et la prise en charge des cas de cytomégalovirus congénitale (CMVc) qu'ont dépistés les pédiatres en pratique clinique quotidienne au Canada.

MÉTHODOLOGIE : Les pédiatres généraux et surspécialisés en pratique clinique au Canada ont participé à la surveillance mensuelle active du CMVc entre le 1er mars 2005 et le 28 février 2008 par l'entremise du Programme canadien de surveillance pédiatrique.

RÉSULTATS : Les pédiatres ont déclaré 49 cas d'infections à CMVc (4,5 cas sur 100 000 naissances) : 40,8 % étaient nés avant 36 semaines d'âge gestationnel, 55,1 % avaient un poids de naissance de moins de 2 500 g et 28,6 % et 30,6 % se situaient sous le troisième percentile de poids et de circonférence crânienne, respectivement. Les mères avaient un âge médian de 23 ans, et 18,4 % avaient moins de 20 ans. Huit mères (16,3 %) étaient d'origine autochtone (prévalence de bébés non autochtones de 3,9 cas sur 100 000 naissances, prévalence de bébés autochtones de 15,8 cas sur 100 000 naissances, P<0,005). La principale anomalie décelée en laboratoire était la thrombocytopénie (53,1 %). Trente-trois nourrissons (67,3 %) présentaient des manifestations neurologiques. De ce nombre, 12 (36,4 %) ont reçu un traitement au ganciclovir et 21 (63,6 %) n'en ont pas reçu.

CONCLUSION : Seule une minorité du nombre prévu de nourrissons symptomatiques infectés par le CMVc a été signalée dans la présente étude. La majorité de ces nourrissons gravement atteints, y compris ceux ayant une maladie neurologique, ne reçoivent pas de traitement au ganciclovir. La présente description des pratiques et du diagnostic actuels fait ressortir la nécessité de parvenir à un dépistage plus complet des cas au sein de la population, de même que de mieux sensibiliser les médecins au traitement optimal de la CMVc symptomatique.

Congenital cytomegalovirus (cCMV) infection is recognized as an important public health problem and the most common congenital infection (1). Numerous studies have documented cCMV infection rates of between 0.3% and 2.2% (1), with a recent review of universal screening programs indicating an overall birth prevalence of 0.7% (2). Studies have determined that the population-based birth incidence of cCMV using universal screening in a Canadian urban centre was 0.4% (3) and population-based incidence of cCMV in high-risk infants was 1.5% (4). While only 12.7% of infected newborns are symptomatic at birth, these infants have a high rate of neurological sequelae, and an additional 13.5% of asymptomatically infected children will experience late sensorineural sequelae, including hearing loss, which may not emerge until months or years later (2,5). The definitive diagnosis of cCMV in these late-presenting infants is hampered by the need to detect CMV in diagnostic specimens within the first 21 days of life because postnatally acquired CMV is common in early infancy (6). Thus, many affected infants are being missed.

Although there are currently no means of preventing cCMV infection, significant progress has been made in understanding the epidemiology and natural history of cCMV infection. The benefits of early diagnosis for early intervention in hearing loss and consideration of intervention with antiviral therapy have been described (7). A National cCMV Disease Registry was established in the United States, which relies on voluntary passive reporting of clinical cases that are primarily symptomatic (8). Paediatricians, primarily in large urban medical centres, voluntarily reported cases and collected data on an estimated 1.7% of all cases of cCMV in

[1]*Department of Pediatrics, Faculty of Medicine and Dentistry, University of Alberta;* [2]*Women and Children's Health Research Institute, Edmonton, Alberta*
Correspondence: Dr Wendy Vaudry, Department of Pediatrics, University of Alberta, Edmonton Clinic Health Academy, 3-588D 11405 87 Avenue, Edmonton, Alberta T8G 1C9. Telephone 780-248-5540, fax 780-248-5627, e-mail wvaudry@ualberta.ca
Accepted for publication June 24, 2013

the United States (9). A significant limitation to this registry is the voluntary, passive nature of case ascertainment from a limited segment of the population. The need for screening programs has been highlighted and controversies have been described eloquently (1,10).

Active surveillance for clinically symptomatic cases has been conducted in both Australia (11) and the United Kingdom (12) through their respective national paediatric surveillance units, and has documented the severity of illness in children identified and the low rates of reported diagnoses. Using active population-based case findings from across Canada, the present study aimed to describe the current practices of paediatricians with respect to the diagnosis and management of cCMV in this country.

METHODS

Study design

From March 1, 2005, to February 28, 2008, national surveillance for cCMV was conducted by the Canadian Paediatric Surveillance Program (CPSP), a national network that surveys >2500 clinically active paediatricians and paediatric subspecialists in Canada for several rare conditions on a monthly basis. The CPSP uses a two-tiered reporting process to ascertain and investigate cases: an initial 'check-off' form (80% response rate) and a detailed reporting form (96% completion rate for the program overall). After receiving a report, the CPSP identifies duplicate reports by comparing birth date, sex and reporting centre of the case. A detailed questionnaire is then mailed to the reporting paediatrician. To protect confidentiality, no personal identifying information was reported to the CPSP, each reported case was assigned a study number and only non-nominal data were collected on the case report form.

The completed questionnaires were collected by the CPSP and forwarded to the principal investigator at the University of Alberta (Edmonton, Alberta), who determined whether the case fulfilled the case definition (confirmed case) or not (excluded case). The reports were kept in locked storage, with access only available to the principal investigator. Paper copies of the case report forms were retained securely by the CPSP for back-up purposes only. The data regarding confirmed cases were entered into a password-protected Access database (Microsoft Corporation, USA) at the University of Alberta. The present study was approved by the Health Research Ethics Board at the University of Alberta.

Case definition

A confirmed case of cCMV was defined as any newborn ≤21 days of age with a positive laboratory test for CMV including viral isolation from the urine or throat; or a positive polymerase chain reaction (PCR) test from a urine, throat or blood specimen; or the presence of CMV-specific immunoglobulin (Ig) M in neonatal or cord blood.

Maternal data collected: Data regarding ethnicity, country of birth, residence in a rural area (population <1000), age, parity, educational level, employment status and type of work were requested. Child daycare exposure was specifically solicited including whether the mother had worked in child daycare before or while pregnant, and whether there was household exposure to children attending child daycare.

Infant data collected: Demographic, clinical and laboratory manifestations of infection, viral diagnostic results, cranial imaging, and assessments in audiology and ophthalmology were collected. A description of antiviral therapy was specifically requested. Outcome data collected included the length of hospital stay, number of days in intensive care and the infant's status at the time of the report (hospitalized, discharged or deceased).

Data analysis

Data were summarized according to frequency (median, range and percentage). The calculation of the birth prevalence was based on cumulative annual population estimates for the period between February 2005 and March 2008 for each province and all of Canada, obtained from Statistics Canada (www40.statcan.ca/l01/cst01/demo04a-eng.htm). Rates for the Canadian Aboriginal population living on and off reserve were calculated based on population data provided by the Department of Aboriginal Affairs and Northern Development Canada. The difference in the prevalence of cases between Aboriginal and non-Aboriginal populations was analyzed using Fisher's exact test. SPSS version 17.0 (IBM Corporation, USA) was used to perform the data analysis. Small for gestational age (SGA) was defined as weight <3rd percentile according to gestational age (GA) and sex, according to the Public Health Agency of Canada standards (13). Head circumference ≤3rd percentile according to GA was determined using raw data from a published meta-analysis that generated new standards (14).

RESULTS

Incidence

Nationally, 118 reports were received during the three-year study period. At least one report was received from nine of the 10 provinces in Canada and none from the Territories. Of the 118 reports, 36 were duplicate reports of the same patient submitted by different paediatricians. The detailed reporting form was sent to the 82 paediatricians who first reported each case and was completed by 79 (96% completion rate). Thirty-three reports were excluded from the analysis, with the most common reason being that the age at diagnosis was >21 days. There were a total of 49 confirmed cases of cCMV reported from eight provinces (national birth prevalence, 4.5 per 100,000). The provincial rates ranged from zero to 13.1 cases per 100,000.

Maternal demographic and pregnancy history

The median age of the mothers was 23 years (range 17 to 41 years), 18% of whom were <20 years of age. Thirteen (26.5%) were primigravida. Thirty-four (69.4%) of the mothers were born in Canada, seven (14.3%) were born outside the country (two immigrated >5 years previously, and three immigrated between one and five years previously). Data regarding employment history, educational status and daycare exposure were collected, but no significant trends were observed. The diagnosis of cCMV was suspected antenatally in 28 (57.1%) of the mothers, either because of maternal serology suggesting primary CMV infection (n=2) or fetal imaging abnormalities (n=26). The newborns were then tested after birth to confirm the diagnosis.

Ethnic origin was reported for 40 (81.6%) of the mothers; 22 (44.9%) were Caucasian and eight (16.3%) were Aboriginal. The non-Aboriginal birth prevalence was 3.9 per 100,000, and the Aboriginal birth prevalence was significantly higher (15.8 per 100,000) (P<0.005). Six (12.2%) of the mothers were from rural areas and four of these mothers were members of First Nations living on reserve, with an Aboriginal on-reserve birth prevalence of 12.6 per 100,000.

Infant clinical and laboratory characteristics

Table 1 summarizes the clinical and laboratory characteristics of cCMV in these infants. The median age at diagnosis was three days (minimum 0 days, maximum 18 days). Forty-eight pregnancies were singleton, and one of the twins in the twin pregnancy was stillborn and was not tested for CMV. Thirty-two infants (65.3%) were male. The median GA was 36 weeks (minimum

26 weeks, maximum 41 weeks) and the median birth weight (BW) was 2210 g (minimum 1055 g, maximum 3678 g). When both parameters were reported, the growth percentiles were calculated. The 14 SGA cases include 12 confirmed as <3rd percentile and two reported as SGA with no BW specified. Similarly, in cases in which both head circumferences and GA were reported, percentiles were calculated. The 15 microcephaly cases include 11 confirmed as <3rd percentile and four with no head circumference specified. Thromobocytopenia (53.1%) was the most common characteristic, with jaundice (36.7%), hyperbilirubinemia (26.5%), rash (24.5%), splenomegaly (22.4%), hepatomegaly (20.4%), anemia (14.3%) and hepatitis (12.2%) reported less frequently.

Neurological findings, including microcephaly and abnormal diagnostic testing (cranial imaging, hearing testing, ophthalmologic assessment), are described in Table 2 in relation to the use of antiviral therapy. Cranial imaging was generally performed starting with ultrasound, with follow-up computed tomography or magnetic resonance imaging (MRI) if abnormal. Two infants without an initial ultrasound had prenatal ultrasounds showing abnormalities. Thirty-three of the infants had neurological involvement defined as either microcephaly and/or abnormal cranial imaging, hearing loss or ophthalmological findings. None of these infants had isolated opthalmological abnormalities. Twelve (36.4%) of the infants with neurological involvement received ganciclovir therapy and 21 (63.6%) did not. Four deaths were reported in the first eight weeks of life. A total of 1130 hospital admission days were reported, with 712 days in the intensive care unit.

A wide variety of viral diagnostic methods were used by different laboratories across the country; however, the case definition required viral isolation or positive PCR from any site, or positive IgM to CMV. The type of sample that tested positive for CMV was reported for all cases: all 49 cases tested positive for CMV in urine samples (testing was performed on amniotic fluid for the one case with in utero diagnosis); six of 12 throat samples, two of seven blood samples and one of 13 cerebrospinal fluid samples collected tested positive for CMV. CMV IgM testing was performed in 21 (42.9%) cases, and only 10 cases were positive. All cases tested using CMV IgM also had at least one sample positive for CMV detection.

TABLE 1
Birth characteristics of 49 infants diagnosed with congenital cytomegalovirus infection

Characteristic	n (%)
Male sex	32 (65.3)
Gestational age <36 weeks	20 (40.8)
Birth weight <2500 g	27 (55.1)
Head circumference <33 cm	28 (57.1)
Clinical characteristics	
Small for gestational age*	14 (28.6)
Microcephaly	15 (30.6)
Jaundice	18 (36.7)
Hepatomegaly	10 (22.7)
Splenomegaly	11 (22.4)
Rash	12 (24.5)
Congenital anomalies†	15 (30.6)
Laboratory results	
Thrombocytopenia‡	26 (53.1)
Hyperbilirubinemia§	13 (26.5)
Hepatitis¶	6 (16.7)
Anemia**	7 (14.3)

Percentages were calculated as a percentage of the total number of reported cases (n=49).<3rd percentile according to growth parameter, sex and gestational age, or according to survey response if parameters were not reported; see text; †Dilated ventricles, multicystic intracranial pathology, thin corpus callosum, periventricular leukomalacia, elevated hemidiaphragm, gastroschisis, situs inversus, complex cardiac with ventriculoseptal defect and hypoplasia of pulmonary veins, small ventriculoseptal defect, thoracic meningomyelocele, horseshoe kidney, hydrocele, inguinal hernia, hydrops and mucolipidosis type II; ‡Platelets <100×10^9/L; §Total bilirubin >200µmol/L; ¶Hepatitis, alanine aminotransferase or aspartate aminotransferase >2× normal; **Hemoglobin <120 g/L*

DISCUSSION

While cCMV infection is recognized worldwide as a significant cause of neurological morbidity in children (15,16), the population-based epidemiology and clinical manifestations of this infection have not been examined in Canada for many years (3). Advances have occurred in several areas of cCMV management in the past 20 years: diagnosis using molecular techniques and new screening methods (17-21); antiviral therapy (22,23); intervention for hearing loss (24); and potential vaccine development (25,26). Given that up to 90% of congenitally infected newborns are asymptomatic at birth (27), documentation of current practice in the paediatric community identifies potential areas for improvement in clinical practice and describes the level of diagnostic sensitivity in the absence of screening programs.

The present study was designed to report and describe the cases that are actually diagnosed in the clinical practice of paediatricians in Canada, where there is no routine screening program in place. Using the 49 confirmed cases reported in the study and the national birth cohort in Canada for the period of the study, we calculated a birth prevalence of diagnosed symptomatic cCMV of 4.5 per 100,000. Variations in provincial birth prevalence of cCMV may be related to higher representation of Aboriginal mothers in some smaller provincial birth cohorts. By comparison, in meta-analyses of universal newborn screening programs, the overall birth prevalence of cCMV has recently been estimated to be 0.64% with 11% symptomatic infections (2,27), and 0.7% with 12.7% symptomatic infections (2), respectively, which would indicate a birth prevalence of symptomatic cCMV disease of 70 to 90 per 100,000. The most recent population-based screening study in Canada (3) documented a birth prevalence of cCMV of 0.42%, with 6.3% of cases being symptomatic, resulting in a birth prevalence of 26 per 100,000 for symptomatic cCMV. The birth prevalence reported in our study was one-sixth what would be predicted from these previously published rates and, interestingly, is almost identical to the sixfold lower than expected rate of reporting in surveillance conducted in the United Kingdom and Ireland (12).

There are several potential explanations for the lower than expected number of reports. The methodology of the study involved voluntary reporting and, although some diagnosed cases may not have been reported, under-reporting is unlikely to account for missing 80% of the diagnosed cases. The CPSP is a well-established program in Canada (28), with excellent participation by most paediatricians in the country. The fact that only paediatricians are surveyed may also have led to some under-reporting if cases were diagnosed by other physicians. Although this may have occurred, particularly in some smaller centres, it is unlikely that a paediatrician would not have been involved in the care of most patients. The most likely explanation for the low reporting rate is missed diagnosis. The clinical signs may be subtle in the majority of cases or delayed in presentation beyond the early neonatal period, when the diagnosis can no longer be made definitively. Even in the setting of active surveillance within a well-established national surveillance program, the present study documents that the diagnosis of cCMV is likely only being made

TABLE 2
Neurological manifestations of congenital cytomegalovirus infection: Investigations and antiviral therapy

Investigation		Abnormal, n (%)	
Cranial ultrasound (n=42)		23 (46.9)	
Cranial computed tomography scan (n=22)		11 (22.4)	
Cranial magnetic resonance imaging (n=11)		9 (18.4)	
Audiology assessment (n=36)		9 (18.4)	
Opthalmology examination (n=39)		6 (12.2)	
Abnormal cranial imaging, audiology or ophthalmology findings	**Microcephaly**	**Ganciclovir treatment**	
		Yes	**No**
Infants with neurological manifestations		33 (67.3)	
Yes	Yes	5	6
Yes	No	7	11
No	Yes	0	4
Total		12	21

Percentages are calculated as a percentage of the total number of reported cases (n=49)

in a minority of severely affected infants. This low rate indicates that even symptomatic cCMV is underdiagnosed in clinical practice, and lack of recognition of symptomatic cCMV does not begin to address the issue of identifying asymptomatic infection.

The majority of mothers giving birth to infants with cCMV were Caucasian, but the next most common ethnic group was Aboriginal women (16%), who comprised only 3.4% of the childbearing population during the study period. The birth prevalence of cCMV was more than three times higher in the Aboriginal population. The reasons for this increased prevalence are unclear and were beyond the scope of the present study. They may include risk factors related to a lower socioeconomic standard of living, such as household crowding, particularly with maternal exposure to young children. This has important implications for health care service delivery in Canada and, potentially, for targeting higher-risk groups for cCMV infection screening.

Thrombocytopenia (53.1%) was the most common clinical abnormality, and was sometimes the only abnormality that prompted diagnostic testing for CMV. Hepatosplenomegaly or rash was present in <25% of cases. A variety of cranial imaging modalities were used, and imaging was abnormal in a majority of cases. Fetal MRI findings have recently been described in some detail (29-31), and qualitative descriptions of newborn MRI and computed tomography findings are provided in Table 2.

CMV was most commonly identified by shell vial culture, with a minority of cases identified by PCR. None of the urine samples tested negative. CMV was reported to be identified in throat swabs in only one-half of the samples with results reported. Although throat swab is usually considered to be a reliable specimen for viral isolation of cCMV despite a lower level of viral shedding compared with urine samples (19), the negative results may reflect inaccurate reporting, specimen collection issues or differences in performance characteristics of detection methods in various laboratories. These factors are less likely to affect molecular testing of saliva, which is extremely sensitive, simple to collect and has been proposed as the screening method of choice (21). Of note, blood specimens sent for CMV identification using PCR were negative five of seven times they were sent. Although PCR from dried blood spots has been proposed as a cCMV screening method (18,32), the concerns regarding lack of sensitivity that have been raised (15,19) are reinforced by the findings of the present study. When neonatal serum was tested for CMV IgM, it was negative more than one-half of the time. This lack of serological response in the fetus has been well described and emphasizes that the traditional 'TORCH' (toxoplasmosis, rubella, cytomegalovirus, herpes simplex virus and HIV) serological screen should not be relied on as a test for cCMV.

Evidence of efficacy of ganciclovir therapy for cCMV infection has been published (20,22), and the use of this agent has been recommended for the treatment of cCMV with neurological signs (23). In the present study, 33 (67.3%) infants had neurological manifestations; however, the majority (63.6%) of these neurologically affected infants did not receive antiviral therapy. This observation suggests that paediatricians may not be aware of the evidence surrounding ganciclovir and the indications for this therapy.

Outcome data for the present study were limited given the short time after diagnosis that reports were solicited. Four deaths were reported, and significant neurological morbidity is expected for this cohort, given the previously published natural history data (15,33-35). The reporting of number of days in hospital was incomplete because the paediatricians only reported days spent in the hospital in which they worked; the majority of the days reported were in the intensive care unit. However, hospitalization costs comprise only a fraction of the true cost of cCMV infection, which causes lifelong disability and ongoing costs to the health care system and society (36). The present study was not designed to collect long-term outcome data on this cohort because reports were unlinked and anonymous, and the protocol did not allow for the collection of longer-term outcome data.

Through a well-established national surveillance program, the present study has documented the current state of diagnosis of cCMV in Canada and suggests that the gap could be filled by a routine screening program. The present study also showed that the infants of Aboriginal mothers may be at higher risk and described the clinical presentation of affected infants, the diagnostic modalities used, and the management and outcome of these cases. The recognition and diagnosis of cCMV infection is challenging when approached as a clinical diagnosis, and currently identified cases likely only represent the severely affected fraction of the true burden of disease in Canada. Because of the spectrum of clinical manifestations and narrow time window for making an accurate diagnosis, many infants are being denied early definitive diagnosis, thus foregoing neonatal antiviral therapy, optimal follow-up and early intervention for hearing loss. Even when the diagnosis is made in infants with neurological disease, paediatricians are prescribing antiviral therapy in only a minority of cases. The findings of the present study have important implications for the education of individuals providing care for newborns and may inform public health policy. Further research should be performed to determine the optimal components of population-based screening and investigate the cost benefit of introducing a cCMV screening program in Canada.

DISCLOSURES: The authors have no financial or other conflicts of interest to declare.

ACKNOWLEDGEMENT: This study was supported by funding from the Public Health Agency of Canada. The authors gratefully acknowledge the contributions of the Canadian Paediatric Surveillance Program and the paediatricians who reported cases of cCMV.

CONTRIBUTORS STATEMENT: Wendy Vaudry conceived of and designed the study, organized the acquisition of data through the CPSP, interpreted the data, drafted and revised the manuscript and approved the final version. Bonita Lee contributed to the study design, analysis and interpretation of the data, revised the manuscript critically and approved the final version. Rhonda Rosychuk contributed to the study design, design of the data base and analysis of the data, revised the manuscript and approved the final version.

REFERENCES

1. Demmler GJ. Screening for congenital cytomegalovirus infection: A tapestry of controversies. J Pediatr 2005;146:162-4.
2. 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.
3. Larke RP, Wheatley E, Saigal S, Chernesky MA. Congenital cytomegalovirus infection in an urban canadian community. J Infect Dis 1980;142:647-53.
4. Vaudry W, Rosychuk RJ, Lee BE, Cheung PY, Pang XL, Preiksaitis JK. Congenital cytomegalovirus infection in high-risk Canadian infants: Report of a pilot screening study. Can J Infect Dis Med Microbiol 2010;21:e12-9.
5. Dahle AJ, Fowler KB, Wright JD, Boppana SB, Britt WJ, Pass RF. Longitudinal investigation of hearing disorders in children with congenital cytomegalovirus. J Am Acad Audiol 2000;11:283-90.
6. Peckham CS, Johnson C, Ades A, Pearl K, Chin KS. Early acquisition of cytomegalovirus infection. Arch Dis Child 1987;62:780-5.
7. Pass RF. Congenital cytomegalovirus infection: Impairment and immunization. J Infect Dis 2007;195:767-9.
8. Demmler GJ. Infectious Diseases Society of America and Centers for Disease Control. Summary of a workshop on surveillance for congenital cytomegalovirus disease. Rev Infect Dis 1991;13:315-29.
9. Istas AS, Demmler GJ, Dobbins JG, Stewart JA. Surveillance for congenital cytomegalovirus disease: A report from the National Congenital Cytomegalovirus Disease Registry. Clin Infect Dis 1995;20:665-70.
10. Engman ML, Malm G, Engstrom L, et al. Congenital CMV infection: Prevalence in newborns and the impact on hearing deficit. Scand J Infect Dis 2008;40:935-42.
11. Munro SC, Trincado D, Hall B, Rawlinson WD. Symptomatic infant characteristics of congenital cytomegalovirus disease in Australia. J Paediatr Child Health 2005;41:449-52.
12. Townsend CL, Peckham CS, Tookey PA. Surveillance of congenital cytomegalovirus in the UK and Ireland. Arch Dis Child Fetal Neonatal Ed 2011;96:F398-403.
13. Kramer MS, Platt RW, Wen SW, et al. A new and improved population-based Canadian reference for birth weight for gestational age. Pediatrics 2001;108:E35.
14. Fenton TR. A new growth chart for preterm babies: Babson and Benda's chart updated with recent data and a new format. BMC Pediatr 2003;16:3-13.
15. Berenberg W, Nankervis G. Long-term follow-up of cytomegalic inclusion disease of infancy. Pediatrics 1970;46:403-10.
16. Adler SP, Nigro G, Pereira L. Recent advances in the prevention and treatment of congenital cytomegalovirus infections. Semin Perinatol 2007;31:10-8.
17. Pang XL, Chui L, Fenton J, LeBlanc B, Preiksaitis JK. Comparison of LightCycler-based PCR, COBAS amplicor CMV monitor, and pp65 antigenemia assays for quantitative measurement of cytomegalovirus viral load in peripheral blood specimens from patients after solid organ transplantation. J Clin Microbiol 2003l;41:3167-74.
18. Barbi M, Binda S, Caroppo S, Primache V. Neonatal screening for congenital cytomegalovirus infection and hearing loss. J Clin Virol 2006;35:206-9.
19. Boppana SB, Ross SA, Novak Z, et al. Dried blood spot real-time polymerase chain reaction assays to screen newborns for congenital cytomegalovirus infection. JAMA 2010;303:1375-82.
20. Oliver SE, Cloud GA, Sanchez PJ, et al. Neurodevelopmental outcomes following ganciclovir therapy in symptomatic congenital cytomegalovirus infections involving the central nervous system. J Clin Virol 2009;46(Suppl 4):S22-6.
21. Boppana SB, Ross SA, Shimamura M, et al. Saliva polymerase-chain-reaction assay for cytomegalovirus screening in newborns. N Engl J Med 2011;364:2111-8.
22. 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.
23. Nassetta L, Kimberlin D, Whitley R. Treatment of congenital cytomegalovirus infection: Implications for future therapeutic strategies. J Antimicrob Chemother 2009;63:862-7.
24. Fowler KB, Boppana SB. Congenital cytomegalovirus (CMV) infection and hearing deficit. J Clin Virol 2006;35:226-31.
25. Arvin AM, Fast P, Myers M, Plotkin S, Rabinovich R; National Vaccine Advisory Committee. Vaccine development to prevent cytomegalovirus disease: Report from the National Vaccine Advisory Committee. Clin Infect Dis 2004;39:233-9.
26. Pass RF, Zhang C, Evans A, et al. Vaccine prevention of maternal cytomegalovirus infection. N Engl J Med 2009;360:1191-9.
27. Kenneson A, Cannon MJ. Review and meta-analysis of the epidemiology of congenital cytomegalovirus (CMV) infection. Rev Med Virol 2007;17:253-76.
28. Ugnat A, Grenier D, Laffin Thibodeau M, Davis MA. The Canadian Paediatric Surveillance Program: Celebrating 15 years of successful paediatric surveillance. Paediatr Child Health 2011;16:203-5.
29. Benoist G, Salomon LJ, Mohlo M, Suarez B, Jacquemard F, Ville Y. Cytomegalovirus-related fetal brain lesions: Comparison between targeted ultrasound examination and magnetic resonance imaging. Ultrasound Obstet Gynecol 2008;32:900-5.
30. Picone O, Simon I, Benachi A, Brunelle F, Sonigo P. Comparison between ultrasound and magnetic resonance imaging in assessment of fetal cytomegalovirus infection. Prenat Diagn 2008;28:753-8.
31. Doneda C, Parazzini C, Righini A, et al. Early cerebral lesions in cytomegalovirus infection: Prenatal MR imaging. Radiology 2010;255:613-21.
32. Barbi M, Binda S, Caroppo S, et al. Multicity Italian study of congenital cytomegalovirus infection. Pediatr Infect Dis J 2006;25:156-9.
33. Pass RF, Stagno S, Myers GJ, Alford CA. Outcome of symptomatic congenital cytomegalovirus infection: Results of long-term longitudinal follow-up. Pediatrics 1980;66:758-62.
34. Griffiths PD, Baboonian C. A prospective study of primary cytomegalovirus infection during pregnancy: Final report. BJOG 1984;91:307-15.
35. Noyola DE, Demmler GJ, Nelson CT, et al. Early predictors of neurodevelopmental outcome in symptomatic congenital cytomegalovirus infection. J Pediatr 2001;138:325-31.
36. Ross SA, Boppana SB. Congenital cytomegalovirus infection: Outcome and diagnosis. Semin Pediatr Infect Dis 2005;16:44-9.