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

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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 cytomegalovirus 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 congénital (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 situent sous le troisième percentile de poids et de circonférence crânienne, respectivement. Les mères avaient un âge moyen 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 thrombocytopenie (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.

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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 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.

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 included 11 confirmed as <3rd percentile and four with no head circumference specified. Thrombocytopenia (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 ophthalmological 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 had also at least one sample positive for CMV detection.

**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 1

**Birth characteristics of 49 infants diagnosed with congenital cytomegalovirus infection**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>32 (65.3)</td>
</tr>
<tr>
<td>Gestational age &lt;36 weeks</td>
<td>20 (40.8)</td>
</tr>
<tr>
<td>Birth weight &lt;2500 g</td>
<td>27 (55.1)</td>
</tr>
<tr>
<td>Head circumference &lt;33 cm</td>
<td>28 (57.1)</td>
</tr>
<tr>
<td>Clinical characteristics</td>
<td></td>
</tr>
<tr>
<td>Small for gestational age*</td>
<td>14 (28.6)</td>
</tr>
<tr>
<td>Microcephaly</td>
<td>15 (30.6)</td>
</tr>
<tr>
<td>Jaundice</td>
<td>18 (36.7)</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>10 (22.7)</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>11 (22.4)</td>
</tr>
<tr>
<td>Rash</td>
<td>12 (24.5)</td>
</tr>
<tr>
<td>Congenital anomalies†</td>
<td>15 (30.6)</td>
</tr>
<tr>
<td>Laboratory results</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia‡</td>
<td>26 (53.1)</td>
</tr>
<tr>
<td>Hyperbilirubinemia§</td>
<td>13 (26.5)</td>
</tr>
<tr>
<td>Hepatitis§</td>
<td>6 (12.2)</td>
</tr>
<tr>
<td>Anemia**</td>
<td>7 (14.3)</td>
</tr>
</tbody>
</table>

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, gastrochisis, situs inversus, complex cardiac with ventricular septal defect and hypoplasia of pulmonary veins, small ventriculoaortic defect, thoracic meningocele, horseshoe kidney, hydrocele, inguinal hernia, hydrops and mucolipidosis type II; ‡Platelets <100×10⁹/L; §Total bilirubin >200µmol/L; ¶Hepatitis, alanine aminotransferase or aspartate aminotransferase >2x normal; **Hemoglobin <120 g/L.
TABLE 2
Neurological manifestations of congenital cytomegalovirus infection: Investigations and antiviral therapy

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Abnormal, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cranial ultrasound (n=42)</td>
<td>23 (46.9)</td>
</tr>
<tr>
<td>Cranial computed tomography scan (n=22)</td>
<td>11 (22.4)</td>
</tr>
<tr>
<td>Cranial magnetic resonance imaging (n=11)</td>
<td>9 (18.4)</td>
</tr>
<tr>
<td>Audiology assessment (n=36)</td>
<td>9 (18.4)</td>
</tr>
<tr>
<td>Ophthalmology examination (n=39)</td>
<td>6 (12.2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Abnormal cranial imaging, audiology or ophthalmology findings</th>
<th>Microcephaly</th>
<th>Ganciclovir treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants with neurological manifestations</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Yes</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Yes</td>
<td>7</td>
<td>11</td>
</tr>
<tr>
<td>No</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>12</td>
<td>21</td>
</tr>
</tbody>
</table>

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

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.
CONTRIBUTORS STATEMENT: Wendy Vaudry conceived of and designed the study, organized the acquisition of data through the CPSF, 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.

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