PROTOCOLS

Congenital cytomegalovirus infection

Principal investigator

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Background

Congenital cytomegalovirus infection (CMV) is the commonest congenital infection affecting from 0.2% to 2.4% of all live births. Approximately 10% of infected infants manifest significant clinical illness in the newborn period with a variety of manifestations, including poor growth, microcephaly, jaundice, hepatosplenomegaly, anemia and thrombocytopenia, and almost all of these infants will go on to have later neurologic sequelae. Even if asymptomatic at birth, approximately 5 to 17% will have neurodevelopmental abnormalities, including sensorineural hearing loss, which may only become apparent in infancy or later in childhood. Congenital CMV infection is a difficult diagnosis to prove retrospectively, as definite diagnosis requires isolation of the virus from the newborn in the first three weeks of life. Diagnosis beyond that age may indicate acquired infection from exposure to virus in the birth canal or breast milk. This infection has devastating consequences and is of great public health significance.

Although there has been significant international interest in congenital CMV, there is minimal Canadian epidemiological data, which is at least 25 years old. Current data specific to our own population is essential in planning intervention practices.

Active surveillance for congenital CMV infection is timely as intervention strategies are on the horizon:

- The National Institutes of Health (NIH) have recommended universal newborn hearing screening for early diagnosis and intervention to improve outcome in congenital deafness. However, this approach would miss much of the deafness caused by congenital CMV, which is progressive and only manifests later in

infancy and childhood. Early diagnosis of congenital CMV would allow appropriate screening for early detection of deafness in these high-risk children.

- The Collaborative Antiviral Study Group of the NIH is actively investigating antiviral therapy for this infection. A multicentre randomized controlled trial of ganciclovir in neonates with neurological manifestations of congenital CMV infection demonstrated improved hearing outcome in the treated group.
- CMV vaccines are currently being developed and some have been assessed in clinical trials. This would allow for primary prevention in CMV susceptible women, analogous to the congenital rubella success story.

Surveillance of congenital CMV infection through the CPSP will help public health policy makers to plan their intervention strategies on a national sampling of the paediatric population.

Methods

Through the established methodology of the CPSP, over 2,500 paediatricians and paediatric subspecialists will be actively surveyed for identified cases of congenital CMV infection. A brief case report form will be completed on all identified cases, which will collect data on demographics, risk factors, clinical presentation, diagnostic confirmation and antiviral treatment.

Case definition

The case definition is determined by the fact that the incubation period for CMV infection is three weeks. Any infection documented after three weeks of age could have been acquired postnatally.

Report all newborns with CMV infection confirmed in the **first three weeks of life** by any of the following laboratory methods:

- Culture of CMV from an appropriate clinical specimen*
- Polymerase chain reaction (PCR) positive for CMV from an appropriate clinical specimen*
- Presence of CMV-specific IgM in the neonatal or cord blood†

* Urine, throat, blood, CSF or tissue biopsy

† Please note that serology (i.e., TORCH screen) is a very poor way of making the diagnosis. Many newborns with congenital CMV do not produce detectable IgM. Viral isolation or identification is the most reliable diagnostic method.

Objectives

- To determine the number of congenital CMV infections recognized by Canadian paediatricians.
- To determine the reason for initiating CMV testing in newborns.
- To describe clinical manifestations and risk factors of infected infants in the newborn period.
- To obtain detailed epidemiological data, including maternal histories on confirmed cases.

Congenital cytomegalovirus infection (continued)

- To describe the virologic method of diagnosis and the current usage of antiviral therapy.

Duration

March 2005 to February 2007

Expected number of cases

Using reported incidence rates and the general Canadian birth cohort, a maximum of 165 symptomatic children at birth is expected.

Ethical approval

Health Research Ethics Board of the University of Alberta

Analysis and publication

The incidence rate of congenital CMV in high-risk newborns will be determined as well as a 95% confidence interval to quantify the associated variability. The Statistical Package for the Social Sciences will be used to obtain these and subsequent analyses. Delineation of the demographics and clinical features of confirmed cases will be done with descriptive statistics. The completeness of surveillance data will be compared to simultaneous active laboratory-based surveillance. This will allow for external validation of the CPSP methodology. Comparisons will also be made between results of similar surveillance done by the Australian and British surveillance units.

Investigators will analyze data, interpret results and provide regular feedback to participants. Final study results will be submitted to a peer-reviewed journal for publication.

Bibliography

Arvin AM, Fast P, Myers M, Plotkin S, and Rabinovich R. Vaccine development to prevent cytomegalovirus disease: Report from the National Vaccine Advisory Committee. *Clin Infect Dis* 2004;39:233-9.

Fowler KB, Dahle AJ, Boppana SB, Pass RF. Newborn hearing screening: Will children with hearing loss caused by congenital cytomegalovirus infection be missed? *J Pediatr* 1999;135(1):60-4.

Kimberlin DW, Lin C-Y, Sanchez P, Demmler G, Dankner W, Shelton M, Edwards K, Jacobs RF, Vaudry W, Wright J, Lakeman FD, Kiell JM, Soong S-J, Whitley RJ, and the NIAID Collaborative Antiviral Study Group (CASG). Effect of ganciclovir therapy on hearing impairment in symptomatic congenital cytomegalovirus (CMV) infection involving the central nervous system: A randomized, controlled trial. *J Pediatr* 2003;143:16-25.

Larke RP, Wheatley E, Saigal S, Chernesky MA. Congenital cytomegalovirus infection in an urban Canadian community. *J Infect Dis* 1980;142(5):647-53.

Yow MD, Demmler GJ. Congenital cytomegalovirus disease – 20 years is long enough. *N Engl J Med* 1992;326(10):702-3.