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Symptomatic infant characteristics of congenital cytomegalovirus disease in Australia

Sian C Munro,[1,3] Daniel Trincado,[1,3] Beverley Hall[4] and William D Rawlinson[1,2,3]

[1]*Virology Division, Department of Microbiology, SEALS, Prince of Wales Hospital, Schools of* [2]*Biotechnology and Biomolecular Sciences and* [3]*Medical Sciences, University of New South Wales and* [4]*Royal Hospital for Women, Sydney, New South Wales, Australia*

Background: Human cytomegalovirus (CMV) is the most common cause of viral intrauterine infection. *In utero* transmission can occur during primary maternal infection, reactivation or reinfection of seropositive mothers.
Objective: To describe the aetiology and clinical features of infants diagnosed with congenital CMV and to document maternal factors that were presented.
Methods: Active national surveillance was initiated in 1999 in collaboration with the Australian Paediatric Surveillance Unit.
Results: Monthly notifications resulted in 70 cases of congenital CMV being identified between 1999 and 2003. Nearly all of the cases were symptomatic with the most common clinical sequelae reported in infected infants being jaundice, thrombocytopaenia, hepatomegaly, petechiae, purpura and splenomegaly. Almost half (43.5%) of the infants had central nervous system (CNS) complications, such as microcephaly, chorioretinitis, sensorineural hearing loss, intracranial calcifications, developmental delay or seizures, with over half presenting two or more CNS abnormalities. Maternal febrile illness was noted in 54.8% of the cases. The majority of mothers were primiparous (46.4%) or secundiparous (39.3%), indicating two different population groups at risk of primary CMV infection.
Conclusion: This study documents symptomatic congenital CMV cases in Australia.

Key words: central nervous system abnormalities; congenital CMV infection; herpesvirus; paediatric surveillance; pregnancy.

Intrauterine transmission of human cytomegalovirus (CMV) has been recognized as the major cause of congenital defects in developed countries for over 20 years.[1–3] Severe cases of congenital CMV disease have been reported from recurrent and reinfections;[4–6] however, most cases are thought to result from primary maternal infections. The clinical sequelae of congenital CMV infections appear to be more severe if maternal infection occurs during first or second trimester.[1,7] Primary CMV infections occur in 0.15–2.0% of pregnant women, with 30–40% of mothers vertically transmitting the virus to the fetus.[1–3,8] Approximately 10–15% of congenital CMV cases are symptomatic at birth, with up to 30% of these cases being fatal. Of the 85–90% of children born with asymptomatic congenital CMV, up to 15% will develop symptoms in later life, the most common being sensoneurial hearing loss.[9]

Infants can also be postnatally infected from transmission during parturition, or after birth, from breast milk, saliva, urine, fomites and other sources.[10] Congenital CMV infection is clinically identified by viral isolation from the infant at birth or within 3 weeks of birth. In postnatal infections the virus cannot be isolated at birth or within 3 weeks of birth and clinical illness is much less common and severe.[10,11]

The epidemiology of CMV is known to vary among countries and among social classes within countries;[12,13] however, the current incidence of congenital CMV in Australia is not known. Early data suggested that the rate of congenital CMV cases in Australia and New Zealand was 0.03%, with one in 4000 of live births being severely affected.[14] This rate is very low when compared to those determined in other countries,[8] and of the 12 symptomatic infants described in the study, almost half (42%) were diagnosed by post-mortem.[14] A second study conducted a year later, indicated that 1.5% of pregnant women in an Australian hospital had a primary CMV infection during pregnancy.[15] This rate of seroconversion is comparable to those seen in other countries;[8] however, no symptomatic infants were identified in this study.[15] A need for information on the pathogenicity, and possible factors affecting the pathogenicity, of congenital CMV infections in Australia has therefore been identified.

In collaboration with the Australian Paediatric Surveillance Unit (APSU), active national surveillance for congenital CMV was commenced in Australia in 1999 and is ongoing. The present study reports on the symptomatic clinical characteristics of congenital CMV cases identified over a 4-year period of national surveillance.

METHODS

Notifications of possible cases of congenital CMV were received through the APSU between January 1999 and December 2002. The APSU is an active surveillance system that gathers national data on conditions that effect children, including communicable diseases and their complications.[16,17] Over 1000 participating physicians, paediatricians and child-health specialists report on the incidence and clinical features of specific childhood diseases, which have been diagnosed according to the project case definition. Participating physicians were sent a monthly email or report card to record any new cases of the conditions listed on the card. The cards were returned to the APSU and the study authors notified of any reported cases, accompanied by contact details of the reporting physician. Data were collected from the reporting physicians by the investigators by means of questionnaires. The questionnaires were de-identified so that patient anonymity was preserved. Physicians not returning the questionnaires were initially reminded by letter and subsequently by telephone.

Correspondence: Dr SC Munro, Virology Research Laboratory, Department of Microbiology, Prince of Wales Hospital, High Street, Randwick, NSW 2031, Australia. Fax: +61 2 93984275; email: munros@sesahs.nsw.gov.au
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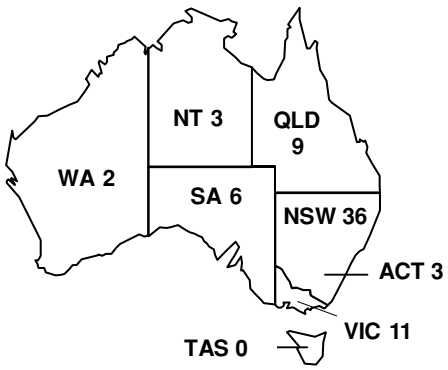

Fig. 1 Geographical distribution of 70 congenital cytomegalovirus (CMV) cases found by means of national surveillance in Australia between January 1999 and December 2002. WA, Western Australia; NT, Northern Territory; SA, South Australia; TAS, Tasmania; QLD, Queensland; NSW, New South Wales; ACT, Australian Capital Territory; VIC, Victoria.

Before the start of the national surveillance, participating physicians were sent an outline of the study and a protocol for reporting cases. A definite case of congenital CMV was defined as a child from whom CMV was isolated in the first 3 weeks of life from urine, blood, saliva or any tissue taken at biopsy. A suspected case was defined as any child up to 12 months of age, from whom CMV was isolated, or who was positive for CMV IgM and in whom clinical features were suggestive of CMV intrauterine infection.[2,11,18] Cytomegalovirus was isolated or detected in laboratories by cell culture, shell vial assays (direct immunofluorscence identification of immediate early CMV antigen)[19] or by histopathological examination of tissue specimens.

RESULTS

Between January 1999 and December 2002, 153 notifications of possible congenital CMV cases were received. Notifying doctors were sent questionnaires, of which 98 (64%) were returned. Of the returned questionnaires, 25 were valid definite cases of CMV, 45 were valid probable cases of congenital CMV, 17 were reporting errors (outside the study limits) and 11 were duplicates (reported by more than one clinician). Of the probable cases of CMV, over half (56%) were suspected of having congenital CMV at birth or within 3 weeks of birth due to the presentation of symptoms. However, viral isolation results were not available within this time frame so the cases were defined as probable rather than definite. Due to this discrepancy in testing and due to the small number of cases identified, the probable and definite cases of congenital CMV were summarized in this study as one dataset of valid cases.

An average of 18 valid cases of congenital CMV were reported annually (17 for 1999, 19 for 2000, 21 for 2001 and 13 for 2002). No seasonal preponderance was noted, nor were any clusters of cases identified. The number of cases from each state of Australia is shown in Figure 1, with nearly half of the cases (51%) occurring in the state of New South Wales (NSW). Six infants were born prematurely at a gestational age of $\leq$35 weeks; 38.6% of the infants were female, 54.3% were male and 7.1% were of unrecorded sex.

Most of the cases of congenital CMV reported (68.2%) were clearly symptomatic at birth or within the first month of life, with only three reports of children diagnosed after 6 months.

Table 1 Clinical symptoms of 62 cases of congential cytomegalovirus (CMV) reported in Australia between January 1999 and December 2002

Clincial symptoms	No. of affected children	% of affected children
Non-neurological abnormality		
Small for gestational age	18	29
Encephalitis	7	11.3
Cataracts	0	0
Microphthalmia	0	0
Splenomegaly	24	38.7
Anaemia	14	22.6
Thrombocytopaenia	26	41.9
Petechiae, purpura	24	38.7
Hepatitis	22	35.5
Hepatomegaly	25	40.3
Jaundice	29	46.8
Pneumonitis	14	22.6
Myocarditis	2	3.2
Undecended testes	0	0
Total affected infants	42	67.7
Neurological abnormality		
Microcephaly	14	22.6
Intracranial calcification	13	21
Seizures	8	12.9
Sensorineural hearing loss	11	17.7
Chorioretinitis	6	9.7
Developmental delay	14	22.6
Total affected infants	27	43.5
Neonatal death	1	1.6
Maternal symptoms		
Maternal illness	34	54.8

From identified cases in which information was provided (88.6%), the reported clinical symptoms are listed in Table 1. Jaundice (46.8%) and thrombocytopaenia (41.9%) were the most common symptoms, with hepatomegaly (40.3%), petechiae, purpura (38.7%) and splenomegaly (38.7%) also frequently reported. Two infants were reported as asymptomatic and one infant had died from CMV-related complications, at the time of notification.

Infants in whom CMV disease had affected their central nervous system (CNS) were considered to be severe cases. Nearly half of the infants (43.5%) had CNS involvement, which was defined as one or more of the following CNS abnormalities: microcephaly, chorioretinitis, sensorineural hearing loss, intracranial calcifications, developmental delay or seizures. In the case where the infant had died, neurological damage was not known.

Where maternal information was provided (84.2%), over half (54.8%) of the mothers had suffered maternal febrile illness during pregnancy, with 30% of these women also CMV IgM positive on serology testing. The child reported with congenital CMV was commonly the first (46.4%) and the only conceived (45.8%) child of the mother. Most of the remaining mothers had conceived twice (25.4%) and given birth to a second child (39.3%). The majority of mothers were born in Australia (80.7%), with individual mothers also born in England, Greece, Indonesia, Ireland, Lebanon, Pakistan, Poland, Sri Lanka, Timor, USA and Vietnam.

DISCUSSION

Symptomatic congenital CMV infection may present with a spectrum of clinical sequelae, which can affect multiple

sites and have significant morbidity and mortality. This study reports on a number of congenital CMV cases that were identified primarily through the presentation of symptoms. The most common symptoms reported in this study were jaundice, thrombocytopaenia, hepatomegaly, petechiae, purpura and splenomegaly. Although the study is based on retrospective data, which will have caused selection bias regarding the severity of symptoms, the findings are consistent with published data seen in other countries.[4,8,18,20,21] The common symptoms reported may cause significant, life-threatening problems; however, they also may resolve without permanent damage to the infant. In contrast, CNS disease in infants may have a permanent effect on the outcome of the child, such as delayed mental development, deafness, seizures, cerebral palsy and blindness.[20–23] Nearly half (43.5%) of the infants reported had CNS complications, with most presenting two or more symptoms. This rate of CNS involvement was lower than that seen in studies in other countries (72%[20] and 68%[18]).

The most common clinical manifestation of primary CMV infection in healthy adults is a mononucleosis-like illness.[24,25] In the current study, 54.8% of mothers noted a febrile illness during pregnancy; however, given the numerous causes of fever, it represents a non-specific indicator of maternal CMV infection. The child reported with congenital CMV was usually the first (46.4%) and only conceived child (45.8%) of the mother, or their second child (39.3%). This distribution suggests that there are two different risk groups, primiparous and secundiparous. Risk groups for CMV infection need to be identified so that they can be taken into account in future studies of congenital CMV, as it is likely that the different risk groups have different sources of infection. It will also be of interest in future studies to observe if the CMV strain[26,27] or the glycoprotein B genotype[28,29] correlates to the different risk groups or the different mechanisms of CMV intrauterine transmission.

Approximately half (51.4%) of the reported congenital CMV cases were from the state of NSW (Fig. 1), with an annual average of nine out of an estimated 78 cases reported (Table 2). The increased report rate for this state may be because NSW has the largest state population in Australia[30] and/or that over one-third of the reporting physicians (38.7%) for the APSU are based in NSW.[17] Risk factors for CMV infection, relating to increased risk of exposure include youth, promiscuity, crowding, poor hygiene, a history of sexually transmitted diseases and increased contact with infants.[13,31–36] Such factors can also be correlated with the socioeconomic status within a community and it has been shown that lower socioeconomic community groups tend to have higher congenital CMV infection rates.[8,13,26,36] The majority of reported cases in NSW were from the south-western area of the city of Sydney, which has a relatively low socioeconomic status.[37] This may have contributed to the increased number of reports from this state.

Table 2 Estimated annual incidence of congenital cytomegalovirus (CMV) infection and disease in Australia and New South Wales (NSW)

Category	Estimated figure in Australia	Estimated figure in NSW
Live births	~246 000†	86 500†
Primary maternal infection rate (1.5%)	3690	1298
CMV infected infants (40%)	1476	519
Symptomatic infection at birth (15%)	221	78
Those with fatal infection (30%)	66	23
Those with severe sequelae (70%)	155	55
Asymptomatic infection at birth (85%)	1255	441
Those with later sequelae (15%)	188	66
Total with CMV sequelae	409	144

†Estimated births in Australia and NSW based upon figures from the Australian Bureau of Statistics.[30]

Based on the primary maternal infection rate of 1.5% described by Sfameni in 1986 and the number of Australian births, it is estimated that there are approximately 1476 babies born with congenital CMV in Australia each year and that 221 of these children will be symptomatic at birth (Table 2). Through active national surveillance 70 cases of congenital CMV were reported over a 4-year period in Australia. This is clearly an underestimate of the true rate of congenital CMV in Australia as the number of participating clinicians limits the study. Many cases of congenital CMV are not diagnosed, especially if the infant is asymptomatic at birth. The rate of diagnosis will only improve through the screening of pregnant women and the educating of clinicians of the relative frequency of this disease. In order to estimate the current rate of congenital CMV within Australia, the study authors are now conducting a prospective study of pregnant women in Australian hospitals.

This study has outlined the extent of damage to those infants congenitally infected with CMV in Australia, and provides the basis for larger prospective studies. As there is no current therapy or vaccine for CMV, the only remaining option to minimize the number of cases of congenital CMV and inform women of their CMV serostatus before, or during pregnancy, by introducing diagnostic algorithms for screening.[38,39] Women at risk can be educated about preventative hygiene measures to minimize their exposure to CMV. Through understanding, diagnosis and education of congenital CMV we can reduce the overall number of children who are born with the serious disabilities outlined in this paper, which are caused by this disease.

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