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Recognition, treatment, and sequelae of congenital cytomegalovirus in Australia: An observational study

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ABSTRACT

Background and objectives: Australian national surveillance data was used to assess recognition, sequelae, and antiviral therapy for congenital cytomegalovirus (CMV) cases.

Study design: Data from congenital CMV cases reported through the Australian Paediatric Surveillance Unit born January 1999 to December 2016 were described and Chi-square tests used to characterise trends and associations in case reporting, maternal CMV serology testing, and antiviral therapy. Descriptive analyses for hearing loss and developmental delay were reported for cases born ≥2004, following introduction of universal neonatal hearing screening.

Results: There were 302 congenital CMV cases (214 symptomatic, 88 asymptomatic). Congenital CMV was suspected in 70.6% by 30 days of age, with no differences across birth cohorts. Maternal CMV serology testing was associated with maternal illness during pregnancy but not birth cohort. There was increasing antiviral use for symptomatic cases, being used in 14% born 1999–2004, 19.6% born 2005–2010, and 44.4% born 2011–2016 ($p < 0.001$). For those born ≥2004, hearing loss was reported in 42.1% of symptomatic and 26.6% of asymptomatic cases; while developmental delay was reported in 16.9% of symptomatic and 1.3% of asymptomatic cases.

Conclusion: There appears to be under-reporting and under-recognition of congenital CMV despite increasing use of antiviral therapy. Universal newborn CMV screening should be considered to facilitate follow-up of affected children and targeted linkage into hearing and developmental services, and to provide population-level infant CMV epidemiology to support research and evaluation of antiviral and adjunctive therapies.

1. Background and objectives

Congenital CMV (cCMV) has an overall birth prevalence of 0.6–0.7%, with approximately 10–15% symptomatic during the newborn period [1,2]. Both symptomatic and asymptomatic newborns remain at risk of long-term sequelae, particularly hearing loss and developmental delay [2]. The mainstay of long-term management remains supportive hearing and developmental interventions [3], with evidence supporting a role for antiviral therapy commenced during the newborn period for infants with symptomatic cCMV [4,5]. Efforts have been made to reach an international consensus and provide guidelines on appropriate strategies for early identification of infants with cCMV, including consideration of universal neonatal screening [6,7].

Currently there is no universal screening for CMV in Australia [8], and diagnosis of cCMV relies on clinician suspicion and investigation, resulting in a small proportion of affected and at-risk infants being identified [9,10]. Targeted testing of at-risk populations results in higher rates of case ascertainment [11,12], as demonstrated in the

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United Kingdom [13]. Australian national surveillance of cCMV has been performed through the Australian Paediatric Surveillance Unit (APSU) since 1999, and results from this study have been previously reported [9,10]. This report aimed to i) analyse trends in case reporting and age at cCMV recognition, ii) evaluate maternal CMV serology testing, iii) determine the burden of hearing loss and developmental delay, and iv) assess trends in antiviral therapy use.

2. Study design

2.1. Study population

Details of the APSU cCMV study have been previously reported [9] and the study protocol published online [14]. In brief, participating clinicians are contacted monthly to record new cases of cCMV. Study investigators are sent contact details of clinicians reporting new cases and a questionnaire is sent to the clinician to record information regarding demographics, clinical features, investigations, and antiviral therapy, as well as maternal demographics, maternal CMV serology results, and maternal symptoms suggestive of CMV disease (fever, rash, flu-like illness) during pregnancy. Reports are reviewed by study investigators to determine whether cases are valid and definite according to the definition below. Surveillance of cCMV commenced in January 1999 and currently around 1570 clinicians are registered to report to the APSU, representing 93% of practising paediatricians in Australia (Suzy Teutsch, Research Fellow, Australian Paediatric Surveillance Unit, personal communication, 17 September 2018). All valid and definite cCMV cases reported to the APSU that were born between January 1999 and December 2016 were included in this study. Ethics approval was obtained through the South Eastern Sydney Local Health District Human Research Ethics Committee (reference 10/104).

2.2. Definitions

A definite cCMV case was defined as any infant with CMV isolated from urine, blood, saliva, or tissue taken at biopsy ≤21 days of age [14]. Congenital CMV was confirmed for children who were not suspected to have cCMV until > 30 days through testing of specimens taking ≤21 days of age (e.g. newborn dried blood spot). Symptomatic cCMV (ScMV) was defined by the presence of one or more of small for gestational age (SGA), microcephaly, intracranial calcifications; or reporting at ≤30 days of age of otherwise unexplained encephalitis, seizures, chorioretinitis, cataracts, developmental delay, hearing loss, thrombocytopaenia, petechiae/purpura, hepatomegaly, splenomegaly, or jaundice. Asymptomatic cCMV was defined as proven cCMV infection with an absence of clinical criteria consistent with ScCMV. Hearing loss within 30 days was defined as ScCMV, to more clearly evaluate hearing and developmental outcomes for those with clinically unapparent cCMV infection as a newborn. Diagnosis of clinical features consistent with cCMV were at the discretion of reporting clinicians. In the event of missing data for age at which clinical signs or symptoms consistent with cCMV were diagnosed, if an infant's age at cCMV suspicion was ≤30 days and had clinical features consistent with ScCMV, then they were determined to have ScCMV. If a child's age at cCMV suspicion was > 30 days and there were no reported SGA, microcephaly, or intracranial calcifications, then they were determined to have AcCMV. Early onset hearing loss was defined as hearing loss reported ≤30 days of age and late onset hearing loss as hearing loss reported > 30 days of age. Early onset developmental delay was defined as developmental delay reported ≤30 days of age and late onset developmental delay defined as developmental delay reported > 30 days of age.

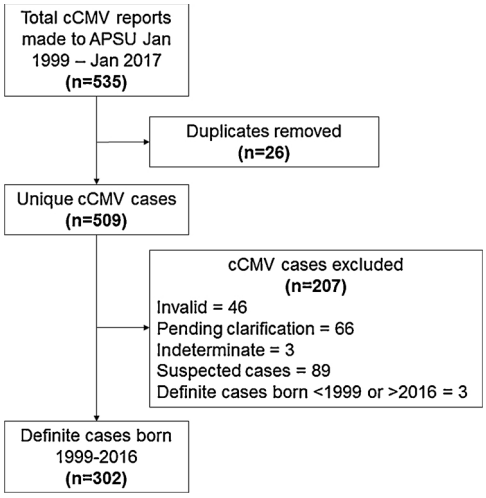

Fig. 1. Case ascertainment from congenital CMV (cCMV) reports made to the Australian Paediatric Surveillance Unit (APSU).

2.3. Statistical analyses

Descriptive analyses were used to report clinical features, maternal serological testing, and antiviral therapy for eligible ScCMV and AcCMV cases, as well as the trend in case reporting over time. Chi-square tests were used to assess for significant associations between categorical variables including: cases suspected ≤30 days of age and birth cohort (1999–2004, 2005–2010, 2011–2016); maternal serological testing and birth cohort; maternal serological testing and symptomatic illness suggestive of CMV during pregnancy; and ScCMV cases who received antiviral therapy and birth cohort. Universal neonatal hearing screening (UNHS) practices became widespread across Australia by 2004 [10]. As such, descriptive analyses for hearing loss and developmental delay were limited to the cCMV cohort born ≥2004 to minimise the impact of undiagnosed hearing loss on developmental delay. All statistical analyses were performed using Stata statistical software, version 14.2 (StataCorp LP, College Station, Texas, US).

3. Results

3.1. Study population and timing of cCMV suspicion

Of the 535 cCMV cases reported to the APSU, there were 302 definite cases born from January 1999 to December 2016 that were included in the study (Fig. 1). Table 1 summarises the characteristics of the study population. For the entire cCMV cohort, there were 231/302 (76.5%) cases suspected ≤30 days of age, 69/302 (22.8%) suspected > 30 days of age, and 2/302 (0.7%) had unknown/missing data. There was no significant difference in the timing of cCMV suspicion across birth cohorts (Table 2).

3.2. Maternal CMV serology testing

Of mothers who delivered 1999–2004, 4/68 (5.9%) did not have serology, 21/68 (30.8%) had antenatal serology, 15/68 (22.1%) had postnatal CMV serology only, and 21/68 (30.9%) had missing data. For mothers who delivered 2005–2010, 15/133 (11.3%) did not have serology, 23/133 (17.3%) had antenatal serology, 32/133 (24.1%) had postnatal CMV serology only, and 63/133 (47.4%) had missing data. Whilst mothers who delivered 2011–2016, 20/101 (19.8%) did not have serology, 30/101 (29.7%) had antenatal serology, 22/101