New Zealand Paediatric Surveillance Unit

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Congenital Cytomegalovirus infection (cCMV) Study

CASE DEFINITION

Infants or children up to 12 months of age with confirmed or probable congenital cytomegalovirus infection, will be eligible to participate.

- A 'confirmed' case of cCMV is defined as laboratory confirmation of CMV infection in the first 3 weeks of life by virus isolation, or detection of CMV DNA in an infant sample.
- 'Probable' cCMV is defined as laboratory confirmation of CMV infection on samples obtained after the first 3 weeks of life and reported clinical features and/or neuroimaging suggestive of cCMV infection.
    - ***Clinical features associated with congenital CMV infection include: prematurity, low birth weight, sensorineural deafness, other neurological abnormalities (encephalitis, microcephaly, developmental delay), seizures, microphthalmia, chorioretinitis, cataracts), hepatitis, hepatosplenomegaly, thrombocytopaenia, pneumonitis or myocarditis***

REPORTING INSTRUCTIONS

Please report any infant or child with confirmed or probable congenital CMV, as per the definitions above.

Please report any patients who you have seen in the last month and that you have not previously reported to NZPSU

INVESTIGATORS (indicate principal investigator by asterisk)

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STATEMENT OF RESEARCH QUESTIONS

The aim of this study is to:

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1) describe the clinical profile and risk factors of children with confirmed and probable cCMV infection reported to the surveillance unit
2) determine whether there have been missed opportunities for early diagnosis which might have enabled antiviral therapy
3) describe the implementation and uptake of postnatal antiviral therapies to reduce neurodevelopmental sequelae (SNHL, developmental delay, CP)
4) determine the feasibility and best practice processes and governance of establishing a register for cCMV in Australia and NZ
5) provide a sampling frame for future research into cCMV

PROPOSED STARTING DATE May 2020

PROPOSED DURATION OF STUDY 2 years

BACKGROUND INFORMATION

Cytomegalovirus, is a herpesvirus that can cross the placenta, infect the fetus, and cause damage to the developing central nervous system. In developed countries it is has been estimated that about 1 in every 200 infants are born with cCMV.[2, 3], of whom about 15% exhibit signs at birth: microcephaly, poor growth, jaundice and retinal scars. Many will go on to have permanent disabilities including deafness, developmental delay, cognitive impairment, epilepsy, and/or visual defects.[1-3] Of the 85% of infants who do not exhibit signs at birth, 10-15% will develop late onset hearing loss, and possibly mild learning and motor impairments.[4]

Currently there is no neonatal screening for cCMV in NZ so the disease burden and long-term outcomes remain poorly defined, and opportunities for prevention and amelioration of disease are lost.[5] Postnatal antiviral agents (e.g. valganciclovir) have been evaluated in infants with confirmed symptomatic cCMV and there is some evidence to suggest they may reduce neurological disabilities in the short term including sensorineural hearing loss and developmental delay.[6] Data on the efficacy of these agents in infants with cCMV and isolated SNHL alone is limited. Consideration of which infected infants warrant antiviral treatment is a rapidly developing field [7,8].

In recently reported APSU findings 1999-2009, 363 cases of confirmed or probable cCMV infection were diagnosed. 90% had symptoms at birth, reflecting the absence of routine newborn screening [9]. Neurological abnormalities were noted in 54%. Because of lack of routine screening and the lack of symptoms in most infected babies, cases are substantially under-ascertained. The same is likely to be true for NZ. No currently available reporting mechanisms collect follow up data on hearing loss or neurodevelopmental disabilities, which may not manifest until later infancy or childhood in infants with cCMV. Recent evidence reported by investigators suggest that cCMV viremia at birth is more prevalent amongst children with cerebral palsy(CP) (9.6%) than previously thought [10]. Similarly a recently published study has reported that children with cCMV were twice as likely to have long-term impairments especially development delays and sensorineural hearing loss [11].

More work is required to define the burden of cCMV disease and investigate the current use and outcomes of available antiviral therapies, to inform the implementation of targeted

screening and preventative measures. This surveillance project is aimed and providing NZ data that will assist in the development of an Australasian congenital CMV register and inform New Zealand recommendations to optimise diagnosis and management of cCMV. In addition the information could be used for work force planning if treated babies require additional follow-up measures

WHY ARE THE PROPOSED RESEARCH QUESTIONS IMPORTANT?

Currently the burden of cCMV disease in NZ is unknown –estimates of seroprevalence and likely fetal infection rates are extrapolated from overseas data.

Congenital CMV has become an area of high interest since the availability of antiviral treatment – the recommendations for patient selection for treatment are likely to change with time so knowledge of potential patient numbers with details of their disabilities will become more important. Treatment will require monitoring of patients for side-effects and by having a registry we would be able to predict healthcare resource requirements.

Currently, offering antiviral therapy to affected infants requires a named patient pharmaceutical application (NPPA) to Pharmac. It is hoped that better understanding of numbers of affected infants and the evolution of international recommendations as to whom should be treated would provide a business case for funding of valgancyclovir under Special Authority waiver.

RESEARCH METHODS

We would aim to compare our surveillance results with cases identified by the National Minimum Dataset (NMDS) using ICD codes for cCMV (P35.1)
Laboratory surveillance may also be used, to assess completeness of case ascertainment eg comparing the numbers of CMV positive specimens in infants under 3 weeks of age with cases reported to the NZPSU.
There is a planned study at ADHB to review the request patterns for Guthrie card analysis for CMV by PCR and we may be able to look at this over the surveillance period as another method of case ascertainment.

Is a follow-up study planned? If yes, please give details.

Data to be used to inform feasibility of development of a national or Australasian registry.

Findings from this research may be used to inform future long-term follow-up studies of children with cCMV. Any future studies will undergo full ethical review by HDEC.

Please outline any other variation in method from conventional NZPSU practice.

Future planned transTasman data sharing.

Are the cases you need for this study seen by the current mailing list?

The majority of symptomatic cases would be seen by paediatricians

If not, who else would need to be mailed?

Otorhinolaryngologists
Newborn hearing Screen service

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3. Munro SC, Trincado D, Hall B, et al. Symptomatic infant characteristics of congenital cytomegalovirus disease in Australia. J Paediatr Child Health. 2005;41(8):449-52.

4. Manicklal S, Emery VC, Lazzarotto T, et al. The "silent" global burden of congenital cytomegalovirus. Clin Microbiol Rev. 2013;26(1):86-102.

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7. Rawlinson, W. D., Boppana, S. B., Fowler, K. B et al, Congenital cytomegalovirus infection in pregnancy and the neonate: consensus recommendations for prevention, diagnosis, and therapy. The Lancet Infectious Diseases 2017;17(6)e177-188

8. Luck, S. E., Wieringa, J. W., Blázquez-Gamero, D et al. Congenital cytomegalovirus a European expert consensus statement on diagnosis and management. Pediatric Infectious Disease Journal 2017;36:1205–1213..

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Congenital Cytomegalovirus Infection

Background

In developed countries it is has been estimated that about 1 in every 200 infants are born with congenital cytomegalovirus(cCMV) infection[1,2]. Fifteen percent exhibit signs at birth: microcephaly, poor growth, jaundice and retinal scars. Permanent disabilities including deafness, developmental delay, cognitive impairment, epilepsy, and/or visual defects. may ensue. Of the remaining 85% asymptomatic infants 10-15% will develop late onset hearing loss.[3,4].

Currently there is no neonatal screening for cCMV in NZ so the disease burden and long-term outcomes remain poorly defined, and treatment opportunities may be missed [5,6] . Postnatal antiviral agents (e.g. valganciclovir) may reduce neurological disabilities in the short term including sensorineural hearing loss and developmental delay.[7] Consideration of which infected infants warrant antiviral treatment is a rapidly developing field.

More work is required to define the burden of cCMV disease and investigate the current use and outcomes of available antiviral therapies, to inform the implementation of targeted screening. This surveillance project aims to provide NZ data to assist in the development of an Australasian cCMV register, and inform New Zealand recommendations to optimise diagnosis and management of cCMV. In addition, the information could be used for work force planning if treated babies require additional follow-up measures

REPORTING INSTRUCTIONS

Please report any infant or child (up to 12 months of age) with confirmed or probable congenital CMV.

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Follow-up of positive returns:

A questionnaire requesting further details will be forwarded to practitioners who report a case.