Universal post-natal screening for CMV – a worthwhile goal?

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Congenital CMV

- Congenital CMV birth prevalence 0.3-1.2%, on average 0.7%
- 12.5% with symptomatic infection, 87.5% with asymptomatic infection
- 40-60% of surviving cases with symptomatic infection develop long-term sequelae
- 20% of cases of asymptomatic infection have long-term sequelae, usually isolated SNHL
- While risks to the individual are lower, overall, more children with long-term sequelae from cCMV (66%) are asymptomatic at birth

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SNHL secondary to cCMV

- Hearing loss occurs in 35% of infected children, 55% of children symptomatic at birth and 20% of cases of asymptomatic infection
- CMV-related hearing loss maybe unilateral or bilateral, mild to profound
- Approximately 30% of cases are profound (40dB threshold or greater) and bilateral i.e. approximately 10% of all cases of congenital CMV infection
- Approximately 50% of hearing loss due to congenital CMV is delayed or progressive i.e. not able to be detected at birth through newborn hearing screening, children with cCMV should be evaluated 6 monthly until at least 5-6 years of age
- Pathogenesis – viral infection of inner ear structures – epithelium and neural tissue, direct viral-mediated injury plus host inflammatory response

- South Australian annual birth cohort is approximately 20,000 therefore would expect 140 cases of cCMV infection per annum
- Would expect 49 cases of deafness secondary to congenital CMV infection per annum in SA, 14 cases of PBHL, half of which will develop subsequent to birth screening
- Compares with 6 cases of congenital hypothyroidism, 8 cases of cystic fibrosis, 1-2 cases of PKU identified through the newborn screening blood spot ("Guthrie Card") test – congenital disorder (30 conditions)
- Accounts for 25% of PBHL (sensorineural), the leading non-genetic cause of SNHL

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Vertical transmission

- Vertical transmission of CMV may follow either primary infection (30-40%) or reactivation (20%) of CMV in the mother during pregnancy
- The risk of severe, long-term sequelae in individual infants is lower in mothers with CMV reactivation but overall, the contribution to CMV-related SNHL is significant
- Infection during the late first to early second trimester seems to be associated with more severe cCMV than infections occurring later in pregnancy
- Diagnosis of maternal infection:
  - >95% of maternal infections are asymptomatic,
  - serological: IgG, IgM, IgG avidity; many flaws in interpretation, maternal infection does not prove fetal infection, routine screening not recommended
- Diagnosis of fetal infection:
  - **Is the fetus infected?** –
  - detection of CMV in amniotic fluid by culture or PCR, after 21 weeks gestation and at least 6 weeks after maternal infection has been diagnosed,
  - high specificity, sensitivity 70-80%, late transmission?
  - Recommended in primary or undefined maternal infection in the first half of pregnancy or where fetal abnormalities suggestive of infection have been detected
  - **Is the fetus symptomatic?** –
  - detection of CMV viral load in amniotic fluid – conflicting results,
  - fetal ultrasound – microcephaly, cerebral abnormalities
- Treatment – CMV hyperimmune globulin? Reduces risk of vertical transmission and severity of disease in infected fetus. ?obstetric complications – pre-term birth
  - High dose oral valaciclovir (8g/day), therapeutic concentrations in fetal and maternal blood, decreased fetal viral load, improved the outcome of moderately affected fetuses (Leruez-Ville) Am J Obs & Gyn 2016)

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Diagnosis of cCMV in neonate

- Gold standard – CMV isolation in urine and/or saliva within the first 2-3 weeks of life
- CMV PCR of urine or saliva allows a rapid turn around time
- Detection of CMV IgM in neonatal serum – only present in 70% of infected babies
- After 2-3 weeks of life, virological and serological tests will no longer distinguish between ante- and peri-natal CMV infection
- After 3 weeks of age, the diagnosis of cCMV can only be suspected on clinical grounds. PCR of blood adsorbed on Guthrie cards forms part of the aetiological work-up of infants and children with established SNHL diagnosed at an age older than 3 weeks
- The amount of CMV in blood is generally much lower than in urine. Therefore duplicate or even triplicate testing is advised to obtain maximal sensitivity when PCR testing dried blood spots (DBS). False positives and negatives can occur. Positives should be confirmed by CMV serological screening of the infant

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Screening Asymptomatic Newborns for cCMV

- SNHL occurs in up to 20% of with asymptomatic cCMV and the majority will have late onset and/or progressive hearing loss.
- Therefore, both routine physical examination and newborn hearing screening will miss many children who develop SNHL secondary to cCMV.
- A combined approach of newborn hearing screening and CMV screening has been proposed to detect those children with asymptomatic cCMV who may be at risk of developing postnatal hearing loss.
- Several methods have been suggested as a screening tool for CMV including blood, saliva and urine samples

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Screening tests for cCMV

- Culture based techniques are not able to be automated and therefore not suitable for mass screening
- Since DBS are collected routinely for newborn metabolic screening of all infants, these may be able to be used for mass screening using CMV PCR assays however DBS perform poorly in this task missing up to 80% of cases, inadequate sensitivity though specificity is high
  - Not all babies with cCMV have detectable CMV DNA in their blood at birth especially those with asymptomatic infection
- Urine specimens can be stored on filter discs but urine samples are harder to collect than saliva samples
- Due to their ease of collection and since high titres of CMV are shed in the saliva of newborns, saliva specimens are an easier and less invasive specimen to collect for newborn CMV screening
- Rapid culture of saliva for CMV: sensitivity of >98%, specificity 100%
- Dried saliva PCR assay: sensitivity 97.4%, specificity 99.9%
- Liquid saliva PCR assay: sensitivity 100%, specificity 99.9%
- Positive screening results should be repeated to rule out occasional false positives
- Greatest potential as a screening tool for cCMV in newborns

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Treatment of symptomatic cCMV

- Physical examination, CBE, LFTs, CMV IgG, IgM, quantitative PCR of CMV-DNA in blood and urine, cranial ultrasound, BAER, fundoscopy
- Microcephaly, hypotonia, hemiparesis, seizures, intracranial calcifications, chorioretinitis, SNHL, hepatosplenomegaly, elevated ALT, petechiae, thrombocytopaenia, IUGR
- Treatment with IV ganciclovir for 6 weeks demonstrated to improve hearing outcomes at 6 months but the benefits wane over time – symptomatic disease involving CNS (2003)
- Treatment with oral valganciclovir for 6 months as compared to 6 weeks did not improve hearing in the short term but improved hearing and developmental outcomes in the longer term – symptomatic disease with or without CNS involvement including SNHL (2015)
- Improvements in hearing at 12 months persisted at 24 months
- Neurodevelopmental testing conducted at 24 months showed improved performance in the language and receptive communication components in the 6 month compared with the 6 week group
- Neutropaenia was the most significant side effect and occurred with approx equal frequency in both treatment groups during the placebo-controlled phase
- Commenced in the first 30 days of life

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Treatment of asymptomatic cCMV

- CMV quantitative PCR showed that higher viral load in blood from newborns, obtained during the first month of life, correlated with a higher likelihood of hearing loss – studies contained mostly cases of symptomatic infection (2005)
- A low blood viral load in asymptomatic children is associated with lower risk of hearing deficit but no viral load threshold associated with SNHL – study contained both symptomatic and asymptomatic children (2009)
- Asymptomatic newborns more likely to experience a late-onset hearing deficit with a viral load in blood >=17000 copies/ml (2014)
- May be able to be used for prognostication and as an indication for treatment
- May be an important complement to newborn hearing screening in early detection and management of hearing loss
- No association between viral load and hearing loss beyond neonatal period

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cCMV screening – a worthwhile goal?

- Importance of SNHL related to cCMV as a public health problem
- Would expect 49 cases of deafness secondary to congenital CMV infection per annum in SA, 14 cases of PBHL, half of which will develop subsequent to birth screening

- Natural history
- Asymptomatic at birth in 87.5% of cases, these cases make the greatest contribution (66%) over time to cases of cCMV –related SNHL

- Availability of reliable, acceptable, low-cost screening tests
- Dried saliva PCR assay: sensitivity 97.4%, specificity 99.9%, cost $25.00 per test, ?eventual addition of blood CMV viral load, ??eventual addition of treatment of asymptomatic neonates with high viral load

- Structures for diagnosis and treatment
- Universal hearing screening program, early provision of hearing aids, cochlear implantation and speech therapy

- Cost vs benefit analysis – annual cost for screening birth cohort - $500,000.00

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