Does screening for congenital cytomegalovirus at birth improve longer term hearing outcomes?

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ABSTRACT

Currently, the diagnosis of congenital cytomegalovirus (cCMV) infection in most highly resourced countries is based on clinical suspicion alone. This means only a small proportion of cCMV infections are diagnosed. Identification, through either universal or targeted screening of asymptomatic newborns with cCMV, who would previously have gone undiagnosed, would allow for potential early treatment with antiviral therapy, ongoing audiological surveillance and early intervention if sensorineural hearing loss (SNHL) is identified. This paper systematically reviews published papers examining the potential benefits of targeted and universal screening for newborn infants with cCMV. We found that the treatment of these infants with antiviral therapy remains controversial, and clinical trials are currently underway to provide further answers. The potential benefit of earlier identification and intervention (eg, amplification and speech therapy) of children at risk of later-onset SNHL identified through universal screening is, however, clearer.

INTRODUCTION

Congenital cytomegalovirus (cCMV) is the most common intrauterine infection in highly resourced countries, occurring in 0.4%–0.64% of all births.^{1 2} The true incidence of the disease is likely to be higher, as up to 90% of infected infants are asymptomatic at birth. Up to 10%–25% of all childhood sensorineural hearing loss (SNHL) is attributed to cCMV infection, making cytomegalovirus (CMV) the largest non-genetic cause of SNHL in children.³ cCMV-related SNHL is progressive in more than 50% of cases.¹ Identification, through either universal or targeted screening of asymptomatic newborns with cCMV, who would previously have gone undiagnosed, would allow for potential early treatment with antiviral therapy, ongoing audiological surveillance and early intervention if SNHL is identified. Early identification of hearing loss is associated with improved language development.⁴ Antiviral therapy has been shown to reduce hearing deterioration in symptomatic children with cCMV if started within the first month of birth.⁵

Our review will address the structured clinical question ‘In asymptomatic newborn infants in highly resourced countries (P), does screening for cCMV using saliva PCR testing (I) compared to not screening (C) allow for earlier identification of infants with CMV-related SNHL and effective early intervention/treatment?’. It will also assess cCMV screening against the WHO screening criteria.

What is already known on this topic?

- Congenital cytomegalovirus (cCMV) is the largest non-genetic cause of sensorineural hearing loss (SNHL) in children.
- cCMV-related SNHL is progressive in more than 50% of cases, and affected infants are likely to pass their newborn hearing screen.

What this study adds?

- Identification, through either universal or targeted screening of asymptomatic newborns with cCMV, who would previously have gone undiagnosed.
- This would allow for potential early treatment with antiviral therapy if other symptoms are identified, ongoing audiological surveillance and early intervention if SNHL develops.

Definitions

The definition of symptomatic cCMV infection varies in the literature.⁶ For the purposes of this review, children are classified as symptomatic if they have acute signs present at birth. These signs include petechiae, jaundice, hepatosplenomegaly, microcephaly (head circumference <2nd centile or 2 SD below the mean), SNHL, small for gestational age (birth weight <10th centile), chorioretinitis and seizures. Targeted screening is defined as screening limited to those children having failed their newborn hearing screen.

Search strategy

MEDLINE via Ovid (1946 to 3 June 2017), Embase via Ovid (1974 to 11 July 2017) and the Maternity and Infant Care Database (1971 to June 2017) were searched for relevant articles. Full search strategies and detailed results are available in the online supplementary data. A total of 124 articles, after removal of duplicates, were found and screened by title and abstract. Twenty-nine full-text articles were subsequently reviewed, and six articles were included as relevant to the clinical question. These are summarised in [tables 1 and 2](#).

Newborn screening for cCMV infection

To allow for better understanding of whether cCMV may be an appropriate condition to screen

Table 1 Universal screening

Citation, country	Study group	Study type (level of evidence)*	Outcome	Key result	Comments
Leruez-Ville <i>et al</i> , ¹⁹ France	11 740 neonates screened with CMV saliva PCR.	Prospective study (3).	Prevalence of cCMV was 0.37% in this population.	51 newborns had a positive screening confirmed infected on subsequent samples. Four of these infants with cCMV were identified to have either unilateral or bilateral hearing loss.	9/44 (20%) of cCMV-positive infants were considered symptomatic. The four infants with hearing loss were included in the larger group of nine symptomatic infants; however, the paper does not indicate whether they had any other features of symptomatic cCMV.
Barkai <i>et al</i> , ²⁰ Israel	9845 infants screened for cCMV by salivary PCR.	Prospective study (3).	Prevalence of cCMV was 0.49% in this population.	56 infants had a positive saliva assay. 47 of these cases were confirmed by urine PCR and culture. Two infants were diagnosed with hearing impairment (late onset in one case).	All 47 infants passed hearing testing successfully prior to hospital discharge. One infant with a hearing loss was detected on further testing done within 23 weeks of age. Another infant was diagnosed with unilateral SNHL at 3 months of age.

CMV, cytomegalovirus; cCMV, congenital cytomegalovirus; SNHL, sensorineural hearing loss.

for in all newborn infants, it will be assessed against the WHO criteria (box 1):

Important health problem

cCMV is recognised as the most common preventable infective cause of SNHL in children and is the leading non-genetic cause of SNHL. It is a significant public health problem.^{7,8}

Accepted treatment or intervention for patients with recognised disease: antiviral therapy

Treatment of newborns with symptomatic cCMV with antiviral therapy has been shown to improve hearing and developmental outcomes. There is evidence that the use of 6 weeks of ganciclovir improves or maintains hearing outcomes at 6 months if started within the first month of life.⁵ A subsequent study demonstrated that 6 months of valganciclovir delivers more sustained improvements in hearing and improves neurocognitive outcomes in newborns with cCMV.⁹

In terms of evidence for treatment of infants with isolated SNHL and confirmed CMV and no other symptoms, there have been no clinical trials to date and expert opinion varies. Many commentators recommend treatment, extrapolating from improved hearing outcomes in treated symptomatic infants.⁷ For a newborn with asymptomatic infection who passes the hearing screen, there is currently no data to support treatment. Similarly, there is no data to support treatment of CMV-related hearing loss presenting or developing beyond the first month of life. All of these patient groups are currently the subject of ongoing clinical trials.⁸

Accepted treatment or intervention for patients with recognised disease: audiological surveillance

In approximately 50% of children with SNHL due to cCMV, hearing loss will be progressive.⁷ Many of these children will be asymptomatic at birth and pass their newborn hearing screen. Early detection of subsequent hearing impairment in this group of children is one of the substantial benefits of universal screening for cCMV. This would allow augmentation of hearing and support for speech and language development at a much earlier age than currently possible.⁴

Facilities for diagnosis, treatment and follow-up should be available

A cCMV screening programme may best be incorporated into existing newborn hearing or metabolic screening programme

infrastructures. Confirmation of the diagnosis of cCMV would need to be made and infants then assessed by a paediatrician or infectious diseases physician. Ongoing follow-up of symptomatic infants with cCMV is currently the responsibility of general paediatricians, infectious disease physicians, audiologists and allied health professionals.

Asymptomatic newborns, identified solely through a universal cCMV screening programme, could either have normal or impaired hearing. The latter group would require paediatric, ear-nose-throat (ENT) surgical and audiological follow-up as currently provided for infants with SNHL. In addition, they would require closer monitoring of other aspects of development during early childhood because of the increased risk of subtle neurocognitive impairments associated with cCMV.

Asymptomatic newborns with normal hearing at birth but positive for CMV would also require initial medical review and increased hearing surveillance.⁷ Approximately 50% of children with SNHL due to cCMV will experience progressive hearing loss.⁷ All children with cCMV should have their hearing tested regularly in early childhood to ensure the early detection of progressing SNHL. Specific recommendations for audiological monitoring are at least every 6 months until age 3 years and then yearly until 6 years old.⁷

Recognisable latent or early symptomatic stage and natural history

Ten per cent of children with cCMV are symptomatic at birth, with characteristic sequelae of petechiae, jaundice, hepatosplenomegaly, microcephaly (head circumference <2nd centile or 2 SD below the mean), SNHL, chorioretinitis and seizures. The remaining 90% of infants with cCMV will be asymptomatic, and 10%–15% of these children will develop SNHL over the first 5–7 years of life. For asymptomatic infants, this is their biggest future risk. As this hearing loss often has delayed onset, only 50% of hearing loss cases are detected in the neonatal period.⁷ A recent systematic review found the cumulative risk of SNHL in children with asymptomatic cCMV with follow-up until 5 years was 7%–11%.¹⁰

Availability and acceptability of a suitable test

A highly specific and sensitive screening test is available for cCMV. CMV PCR¹¹ using salivary sample collection is more convenient than urine collection, and CMV viral loads are highest in saliva. Sensitivity is reported at 97.4%–100% and specificity at 99.9 compared with rapid culture.² High volume testing using

Table 2 Targeted screening

Citation, country	Study group	Study type (level of evidence)	Outcome	Key result	Comments
Kawada <i>et al.</i> , ²¹ Japan	Infants who had abnormal hearing screening results or other clinical abnormalities suggestive of cCMV. 158 infants in cohort: 127 who had abnormal hearing test results.	Prospective cohort study (3).	6/127 (5%) infants with abnormal hearing results were CMV positive. 3/31 infants with other clinical abnormalities were CMV positive.	Six infants identified with cCMV infections also had SNHL. These infants also had central nervous system imaging; two had white matter abnormalities and two had ventriculomegaly. All positive infants were treated with valganciclovir for 3 weeks. However, only one case had improved hearing following treatment at 1 year.	This study included a large cohort of 20 760 newborns undertaking hearing screening. Only 127 patients were referred for further audiological assessment.
Diener <i>et al.</i> , ²² USA	Infants who failed their newborn hearing screening. 509 infants in cohort. 234 underwent cCMV screening within first 21 days of life.	Retrospective cohort study (4).	14/234 (6%) infants were CMV positive.	6/14 cCMV positive infants (42.9%) had hearing loss: three SNHL, two conductive hearing losses, one mixed hearing loss.	2/6 cCMV-positive infants with hearing loss had conductive hearing loss only, unlikely to be the result of cCMV.
Williams <i>et al.</i> , ¹² UK	Infants <22 days old who were referred for further audiological testing after routine newborn hearing screening programme testing. Known cCMV (symptomatic at birth) cases excluded. 411 infants screened for cCMV with salivary and urine PCR.	Prospective cohort study (3).	Assessment of feasibility (ability to take the samples before 3 weeks of age and clinical assessment by 30 days of age). Assessment of the acceptability (maternal anxiety) of targeted CMV testing of infants referred for further audiological testing.	Six infants (1.5%) were diagnosed with cCMV on salivary samples. Three of these infants had cCMV-related SNHL and were treated with 6 weeks of valganciclovir. 407 infants (99%) returned a sample; 98% of these had salivary swabs returned within 3 weeks. No report of increased maternal anxiety in those with infants screened for cCMV.	Lack of maternal anxiety identified could be attributed to self-selection bias.
Kadambari <i>et al.</i> , ¹³ UK	Infants who had failed their newborn hearing test and <22 days old. 203 infants screened for cCMV by salivary PCR.	Prospective cohort study (3).	Assessment of the feasibility to introducing targeted screening for cCMV for infants who fail their primary newborn hearing test.	2/203 were identified with cCMV. These two infants were seen at 10 days of age by the paediatric infectious disease physicians. One of these infants had bilateral SNHL and was treated with 6 months of valganciclovir.	All audiologists involved agreed performing screening was feasible. 80% of parents of infants referred for further audiological assessment agreed to participate in the screening. Small sample size may not properly assess acceptability of the test to families.

*OCEBM Levels of Evidence Working Group. The Oxford Levels of Evidence 2. Oxford Centre for Evidence-Based Medicine. <http://www.cebm.net/index.aspx?o=5653>.
 CMV, cytomegalovirus; cCMV, congenital cytomegalovirus; SNHL, sensorineural hearing loss.

Box 1 Wilson and Jungner screening criteria²³

- The condition sought should be an important health problem.
- There should be an accepted treatment for patients with recognised disease.
- Facilities for diagnosis and treatment should be available.
- There should be a recognisable latent or early symptomatic stage.
- There should be a suitable test or examination.
- The test should be acceptable to the population.
- The natural history of the condition, including development from latent to declared disease, should be adequately understood.
- There should be an agreed policy on whom to treat as patients.
- The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
- Case-finding should be a continuing process and not a 'once and for all' project.

commercial or inhouse assays is feasible. Australian estimates are that salivary PCR test will cost \$A25.00. Confirmatory testing will be required to confirm the diagnosis and eliminate false positives. Shedding of the CMV virus occurs for long periods of time, so there is an adequate window of time for confirmatory testing. However, if treatment with antiviral agents is being considered, then testing and confirmation of diagnosis would need to occur within 30 days of birth (*see treatment below*).

In the UK, salivary screening for cCMV within the newborn hearing screening programme was found to be feasible, acceptable and identified infants with cCMV-related SNHL.¹² Only infants who failed their initial newborn hearing screen were tested, and feasibility was defined as the ability to take samples before 3 weeks of age and clinical assessment by 30 days of age. Maternal anxiety levels at referral and 3 months later were not increased.¹² The study reported that 98% of the study population successfully provided a salivary swab within the 3-week period. Kadambari *et al.*¹³ included an assessment of the feasibility of introducing targeted screening within the UK, and all healthcare professional involved agreed it was feasible to introduce a targeted screening programme. The acceptability of either targeted or universal screening for CMV to families would need to be addressed during the development of potential programmes.

All individual studies included in this review (tables 1 and 2) used salivary PCR as the screening tool. All demonstrated that introducing either universal or targeted screening programmes was feasible.

Agreed policy on whom to treat as patients: antiviral therapy

This area remains controversial with respect to antiviral treatment. Many recommendations are based on varying expert opinions. Our recommendations, on review of the evidence-base, for which infants would benefit from antiviral treatment would be:

- In symptomatic newborns (<30 days of age):
 - If child is severely unwell, initial treatment with intravenous ganciclovir (not for >6 weeks). Treatment should then be continued with oral valganciclovir to complete a total course (intravenous/oral combined) of 6 months.
 - If child is well/mildly unwell and able to tolerate oral therapy, treatment with oral valganciclovir for 6 months

has been shown to have better hearing and developmental outcome at 12 and 24 months of age.⁹

- ▶ Asymptomatic newborns (<30 days of age): no treatment.
- ▶ Asymptomatic newborns with SNHL (<30 days of age): no currently available data to support treatment; some experts consider treatment up to 6 months with oral valganciclovir.¹⁴
- ▶ Children with CMV-related SNHL identified or developing beyond the neonatal period: no currently available data to support treatment.

Agreed policy on whom to treat as patients: increased audiological surveillance

The potential positive impact on hearing outcomes through implementation of increased surveillance of asymptomatic newborn identified with cCMV through a screening programme needs to be considered.

Cost-effectiveness of targeted and universal screening

A recently published study has assessed the cost-effectiveness of implementing targeted or universal screening for cCMV, relative to no screening in the USA.¹⁵ Costs included the direct costs to the healthcare system, and a number of outcomes were assessed. The study estimated an incremental cost of US\$10 000 per case of cCMV infection detected, US\$90 039 per case cCMV hearing loss detected and US\$12 620 277 per cochlear implant avoided for universal screening, and US\$2832 per case of cCMV infection detected, US\$3 916 per case cCMV hearing loss detected and US\$271 947 per cochlear implant avoided for targeted screening.

A study in the UK estimated the additional cost of 'protecting' hearing in one infant using a targeting screening programme. Based on a valganciclovir treatment efficacy rate of 47%, the study estimated it would cost £14 202 to improve the hearing of one infant.¹⁶ In order to provide more comparable results, future cost-effectiveness studies should estimate quality-adjusted life year outcomes associated with different treatment options. This would be in align with reporting recommendations of medical service appraisal committees internationally.^{17 18}

DISCUSSION

Currently, diagnosis of cCMV infection in most highly resourced countries is based on clinical suspicion, meaning only a small proportion of cCMV infections are diagnosed.

Universal screening

Universal newborn screening would aim to identify asymptomatic infected infants for ongoing monitoring for delayed-onset hearing loss and appropriate follow-up. This hearing loss will not be detected by existing newborn hearing screening protocols. Table 1 outlines two prospective cohort studies examining universal screening for cCMV and follow-up with hearing screening. Leruez-Ville *et al*¹⁹ identified 4 out of 51 newborns with cCMV who had hearing impairment detected on further audiological assessment. This study raised the possibility of detecting false positives when using salivary PCR for screening through postbirth contamination (CMV being often present in breast milk and in the birth canal). Eighty-seven infants in the study were detected as positive for cCMV on their first screen, but on repeat salivary PCR screening, only 51 newborns were confirmed as being truly positive for cCMV. Barkai *et al*²⁰ conducted a universal screening programme and found 2 of 47 infants with hearing loss, one of these being late onset. All infants had normal initial hearing screening results; however,

infants with cCMV were followed up with later audiological assessments.

Targeted screening

Table 2 includes four studies looking at targeted screening for cCMV. All of these studies screened infants who failed their initial newborn hearing screen. One prospective cohort study²¹ identified six infants with cCMV and SNHL. All infants were treated with valganciclovir for 6 weeks, with only one child experiencing an improvement in hearing at 1 year of age. Williams *et al*¹² included an assessment of the feasibility and acceptability of targeted screening and found no increase in maternal anxiety in infants screened for cCMV. They reported that 98% of the study population provided a salivary swab within the 3-week period. Kadambari *et al*¹³ included an assessment of the feasibility of introducing targeted screening within the UK, and all healthcare professional involved agreed it was feasible to introduce a screening programme. Diener *et al*²² evaluated the success of a targeted cCMV screening programme and found that with the introduction of targeted cCMV screening, timely diagnostic hearing evaluation rates improved, from 56% to 77%. The four studies evaluating a targeted screening approach acknowledged the limitations of targeted screening missing those infants who pass their initial hearing test. The main reason for not advocating for universal screening was limited knowledge about the feasibility and cost-effectiveness of such a screening strategy.

To summarise, screening for cCMV infection could result in: (1) increased recognition of mildly symptomatic infants (*universal screening*), (2) diagnosis of cCMV in infants with known SNHL (*targeted screening*) and (3) increased detection of asymptomatic infants at future increased risk of SNHL (*universal screening*). In group one, there is sufficient evidence to support the treatment of mildly symptomatic infants.^{5 9} In group two, it is clear that infants with SNHL will significantly benefit from audiological amplification and appropriate speech and language intervention. However, there is no clear evidence that antiviral therapy will improve outcomes for infants with isolated SNHL secondary to cCMV. Further research is needed to answer this question and this is underway.⁸ For group three, the length of time and frequency of audiological follow-up of cCMV positive asymptomatic infants without SNHL would require consideration. Current recommendations are up until 6 years of age.⁷

Universal screening would identify all three groups previously outlined. Targeted screening would lead to identification of infants in group two and potentially some infants with other symptoms in addition to SNHL.

CONCLUSIONS

In answering our research question 'In asymptomatic newborn infants in highly resourced countries (P), does screening for cCMV using saliva PCR testing (I) compared to not screening (C) allow for earlier identification of infants with CMV-related SNHL and effective early intervention/treatment?', we conclude that *universal screening* would allow for earlier identification of infants with at risk of CMV-related isolated SNHL. Unfortunately, the treatment of these infants with antiviral therapy remains controversial, and clinical studies are currently underway that will hopefully provide evidence of treatment efficacy. Other benefits (early intervention and hearing augmentation) of early identification of hearing impairment in these children at risk of later-onset SNHL, are well documented.⁴

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