Topic Proposal: Targeted Screening for Congenital Cytomegalovirus (CMV)

Type of screening programme: Targeted

Abbreviations:

CMV	cytomegalovirus
cCMV	congenital cytomegalovirus
NHS	newborn hearing screen
NHSP	Newborn Hearing Screening Programme
SNHL	sensorineural hearing loss
RCT	randomised controlled trial
PID	paediatric infectious diseases
FU	follow up
CNS	central nervous system

Summary of your proposal and why the topic is within the remit of the UK NSC (up to 200 words)

We propose a targeted screening programme for congenital CMV (cCMV) using saliva swab testing for all newborns who do not pass their newborn hearing screen (NHS) and are referred for diagnostic hearing tests. The purpose of this programme is to detect cCMV as a cause of sensorineural hearing loss (SNHL) in time for the infant to benefit from oral antiviral treatment which improves hearing and neurodevelopmental outcomes. Randomised controlled trials have shown that the antiviral treatment is only effective if started in the first month of life. However, diagnosis of SNHL following the NHS, and tests to investigate the cause of the hearing loss, are invariably carried out too late, depending on local availability. Targeted screening would enhance the current NHS pathway through prompt detection of neonates with cCMV, enabling affected infants to be fast-tracked for earlier diagnostic hearing tests and assessments, prior to considering treatment. Detecting cCMV in the newborn period would enhance audiological management, minimise the need for hearing aids and cochlear implantation, and reduce health inequalities. A national targeted screen for cCMV would ensure equal access to timely diagnosis and treatment of affected newborns with hearing loss across all regions.

Summary, using published evidence, of the condition, the test and the treatment (up to 500 words)

The condition

cCMV is the commonest congenital infection and affects 1 in 2-300 live births in the UK. Only 10% of infants show overt symptoms and/or signs at birth, (called 'symptomatic'), to prompt CMV testing, and the 90% who do not, (called 'asymptomatic'), mostly go undiagnosed in the absence of any routine screening. It is the commonest non-genetic cause of SNHL and a leading cause of developmental delay in children. Congenital CMV is also the only cause of SNHL for which there is a medical treatment. Approximately, half of affected children have hearing loss at birth, and the rest occur mostly in early childhood. The hearing loss gets worse in half of cases and some children require cochlear implants, with significant impact on children, their families and associated costs to healthcare and society. In 2018, the estimated annual cost of managing infants with cCMV and their long-term sequelae in the UK was £732 million.

The test

Diagnosis of cCMV requires a sample taken within the first three weeks of life to confirm congenital infection. A saliva swab can detect CMV genetic material (DNA) using polymerase chain reaction (PCR). It is a quick, easy and painless sample to take. The swab is placed inside the infant's mouth to absorb saliva and then placed in a sealed container. Large studies, conducted over the last decade, have shown that saliva swabs have almost 100% sensitivity and specificity. Published data from the U.K. shows that it is feasible for newborn hearing screeners to take saliva samples. Moreover, targeted screening was highly acceptable to parents of babies who had a swab taken.

The treatment

This includes three components and follows national audiological and infectious diseases guidance:

1. *Antiviral treatment*. A liquid called valganciclovir is taken by mouth, once all diagnostic tests are completed and after consultation with a paediatric infectious diseases specialist. Randomised controlled trials have shown benefit to hearing and neurodevelopmental outcomes when treatment is started within the first 4 weeks of life. In a minority of infants, full blood count and liver function can be affected whilst on valganciclovir, so bloods tests are done by paediatricians to monitor this.

2. *Early hearing loss and development.* The management of hearing loss can be tailored to the diagnosis individually for each infant i.e. enhanced monitoring for worsening hearing loss, early referral for hearing aids and cochlear implants, and other interventions. Monitoring for other neurodevelopmental effects of cCMV is also very important, such as damage to the balance organs, motor function, vision, cognitive and communication problems, and developmental delay.

3. *Late hearing loss and development.* Ten to fifteen percent of infants with 'asymptomatic' cCMV, develop SNHL in childhood, so identified infants with cCMV and normal hearing receive audiological follow-up until age 6 years to avoid delay in diagnosis of SNHL, and the adverse effects of delayed diagnosis on speech and language, development and education.

Randomised controlled trial (RCT) evidence showing benefit from screening

The RCT evidence for treatment using ganciclovir, and its oral prodrug, valganciclovir, stems from the international published studies done in the U.K. and USA over the last two decades. The primary outcome measure in each of these trials was hearing: there was statistically significant benefit to hearing in treated children compared with non-treated children when antiviral therapy was started in the first month of life. Although participants had symptomatic cCMV with central nervous system (CNS) effects, rather than isolated SNHL, SNHL is considered a CNS effect of cCMV, and children presenting with SNHL are sometimes found to have symptoms of cCMV that have gone undetected, including MRI brain abnormalities. The 2015 RCT provided evidence for additional benefit with a 6 month duration of oral valganciclovir treatment (compared with 6 weeks), plus some improvement in neurodevelopmental scores.

Of note, a recent placebo-controlled RCT of valganciclovir for children with CMV-related SNHL age 4 weeks to 4 years, did not show benefit to hearing, making it even more important to diagnose cCMV within the 4 week period (reference: Clinical Trials.gov identifier: NCT01649869).

Saliva swab CMV PCR testing has been extensively tested both in the controlled conditions of the laboratory, and in multi-centre screening studies of up to 35,000 newborns. The sensitivity ranged from 97.5-100% and specificity was 99.9%. In the UK, studies of screening for CMV in infants referred from the NHS found that

saliva swabs were more practical than urine samples and delivered a result in time to start treatment within the therapeutic window. Additionally, CMV testing was acceptable to parents and the newborn hearing screeners carrying out the test. There was no significant increase in parental anxiety associated with addition of the CMV test to the NHS, or with audiological follow-up.

Internationally, large-scale studies of targeted screening in infants referred from the NHS show that the CMV test identifies infants eligible for treatment, (whose cCMV infection would otherwise have gone undetected, and untreated for eligible cases), within the critical 4 week treatment window.

UK Experience of Targeted CMV Screening

The above evidence has supported the implementation of newborn hearing screener-led early detection pathways in some UK regions, which have been working smoothly, with manageable workload, for several years now. In the East of England this pathway has led to one baby diagnosed and treated within the recommended timeframe per 400 swabs. Newborn screener-led CMV saliva swab pathways have also been in operation in the NW of England for several years. Both teams have presented posters on their pathways, are agreeable to sharing protocols, newborn screener training resources and parent information. An additional benefit has been earlier investigation and identification of other causes of hearing loss which are important to identify early (e.g. genetic neurodegenerative disorders). Earlier CMV testing has also led to fewer Guthrie card CMV tests (which are needed for any child diagnosed with a SNHL after age 3 weeks) which is a cost saving.

Meanwhile, in the USA, targeted screening for cCMV for infants 'failing' their newborn hearing screen has been implemented, and/or mandated by law, in some states, so that eligible children do not miss out on the opportunity of treatment.

The evidence-based management of children for both 'symptomatic' and 'asymptomatic' cCMV is well established in the UK, (and is consistent with international consensus from the European Congenital CMV Initiative).

Compelling evidence for early intervention for SNHL provides the rationale for the NHSP, established in 2006, and for targeted audiological follow-up for risk factors, including cCMV. Targeted screening for congenital CMV also aims to improve audiological, and developmental outcomes, and reduce current health inequalities. Therefore, a targeted cCMV screen is complimentary to aims of the NHSP, and relevant to the NSC's terms of reference.

References

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Flowchart:

Based on NHSP figures for England 2021-2022 and an incidence of cCMV of 1 in 200-300 children

(please see abbreviations list for reference above)