Congenital CMV: current and future research in the UK

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Congenital CMV is the most common congenital infection and a leading cause of sensorineural hearing loss. We describe the current research studies being conducted in the UK that are looking at integrating screening for congenital CMV into the Newborn Hearing Screening Programme and developing more effective antiviral treatment.

A recent global review showed approximately 0.7% of children worldwide are born with congenital cytomegalovirus (cCMV) infection. Studies have shown that the 11% of babies with signs and symptoms from cCMV identified at birth are at highest risk of permanent neurodevelopmental impairment including sensorineural hearing loss (SNHL), intellectual and developmental disabilities. A further 13% of children who are asymptomatic at birth, may develop later impairments, primarily SNHL. Over half of all hearing loss caused by congenital CMV occurs amongst babies who have no symptoms at birth. Congenital CMV accounts overall for approximately 20% of moderate to profound bilateral hearing loss. It is the most common nongenetic cause of SNHL and the only potentially treatable cause. CMV related hearing loss can be either unilateral or bilateral but can cause severe progressive loss. SNHL most frequently affects children under the age of 3, coinciding with the critical period for speech and language development. The SNHL caused by cCMV is often progressive, worsening through early childhood.

Antiviral treatment has been shown in a Randomised Control Trial to prevent further hearing loss and improve developmental outcomes when started in the first month of life in babies born with central nervous system (CNS) disease. At present in the UK testing for cCMV only occurs after a baby is confirmed with hearing loss, and this typically occurs too late for treatment to be offered or effective.

BEST study (The Benefits, feasibility and acceptability of Extended Screening Testing in newborn babies who are referred for further hearing assessment after their neonatal screen)

Screening for cCMV in the UK is not currently performed. Detecting CMV using CMV DNA PCR on Dried Blood Spot (Guthrie) cards has been shown to be insensitive. Testing saliva using CMV PCR is nearly 100% sensitive for detection of the virus but there is currently no NHS clinical or laboratory framework to take saliva samples from every baby at birth and rapidly process them. Integrating saliva testing for cCMV into the routine newborn hearing test could potentially identify affected newborns that could be treated within the time during which treatment is known to work. This may reduce the overall burden of childhood deafness (and developmental disability), and overall costs to the NHS.

The BEST study was funded by the charity Sparks (http://www.sparks.org.uk). Recruitment commenced in Newcastle in August 2010 and south west London in April 2011. Newborns being referred for further audiological evaluation after their initial Newborn Hearing Screen Programme (NHSP) were identified by hearing screeners and parents were contacted by a study co-ordinator. After obtaining verbal consent over the phone, study packs were posted to parents. The study pack contained a saliva swab, urine collection pack, instructions to take samples, consent form and standardised anxiety and ease of use questionnaires. During the first 12 months of the BEST study, of 14,389 newborns, 351 were “referred” for further hearing testing after their initial hearing screening and 248 families were approached with 152 (61%) agreeing to cCMV screening. Five were positive, all known in time to allow assessment for treatment within 28 days. Salivary samples were clearly easier for families with 95% (145) returning salivary samples, all of which were suitable for processing. Only 49% (74) of urine samples were returned of which 15% (11) were not processed as they had leaked in transit. 97% of parents preferred salivary sampling: 71% rated salivary samples ‘very easy’ to collect compared to only 18% for urine samples. Anxiety scores were not significantly different to reference mothers. However, only just over 45% of eligible participants were recruited into the study due to the inherent problems with postal recruitment. The BEST study has demonstrated that targeted screening for cCMV using saliva swabs is feasible and acceptable to parents. The study finished in March 2013 and the results will be published later this year.
BEST 2 study (The Benefits of Extended Screening Testing for congenital CMV – Enhancing clinical Integration with the Newborn Hearing Screening Programme)

BEST 2 aims to assess the feasibility of clinically integrating screening for cCMV into the NHSP. BEST 2 will build on the BEST study, but will now ask the newborn hearing screeners to take the saliva samples at the point of referring newborns to audiology after their initial hearing screen. We anticipate that if a larger number of newborns with cCMV will be detected through BEST 2, thus enabling antiviral treatment to be started appropriately in the first month of life. Babies with congenital CMV, in whom SNHL is not confirmed, would require regular monitoring in case they develop late onset hearing loss.6 We aim to commence recruitment into BEST 2 by October 2013 across south west London for a 12 month period.

CASG 112 (A Phase III, randomised, placebo controlled, blinded investigation of six weeks vs six months of oral ganciclovir therapy in infants with symptomatic congenital cytomegalovirus infection)

Intravenous ganciclovir therapy has been used to treat cCMV for the last twenty years.7 Only one phase III randomised trial by the National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group (CASG 102 study) has been conducted to assess the outcome of ganciclovir treatment in symptomatic congenitally affected infants.4 The study showed that treatment prevented hearing deterioration at 6 months and 1 year of life in infants with CNS involvement. Moreover, infants were shown in a follow up study to have reduced developmental delay at 6 and 12 months of age compared to untreated infants.8 Ganciclovir therapy however has been shown to cause abnormalities in white cells, requires prolonged hospital admission and is associated with line related problems including sepsis and thrombosis.

Valganciclovir is the oral prodrug of ganciclovir. Valganciclovir has been licenced by the US Food and Drug Administration to treat CMV disease in high risk heart or kidney transplant patients and as an off licence infection to treat cCMV disease in Europe. Valganciclovir is an oral syrup which can be administered by parents at home. To date no studies have looked at comparing the efficacy and safety of valganciclovir to ganciclovir in cCMV affected babies. A placebo-controlled, double blind, randomized study comparing 6 weeks versus 6 months of oral VGCV conducted by the Collaborative Antiviral Study Group (CASG 112) closed to recruitment in the UK and USA in June 2013 (http://clinicaltrials.gov/ct2/show/NCT00466817). The primary objectives of the study were to compare hearing outcomes, safety profiles, assess neurological outcomes and monitor CMV viral loads in symptomatic neonates up to one month of life who received 6 weeks versus 6 months of VGCV. The results will be available from late 2013 and may be a significant advance in managing cCMV.
CAGS 403 (A Phase II randomised and controlled investigation of six weeks of oral valganciclovir therapy in infants and children with congenital cytomegalovirus infection and hearing loss)

In the absence of any screening programme, the majority of CMV related SNHL is detected only when investigations are performed in a child identified with hearing loss in infancy or early childhood. No treatment studies have been conducted to assess the effectiveness of starting antiviral treatment to infants after the first month of life when the great majority are diagnosed. The CAGS 403 study is aiming to open to recruitment across 17 sites in the UK and USA by the end of 2013 (http://clinicaltrials.gov/ct2/show/NCT01649869?term=congenital+cmv&rank=7). The primary objective of the study will be to assess the hearing outcomes in infants aged between one month and 3 years with diagnosed cCMV and SNHL and who are randomised to receiving six weeks of valganciclovir therapy or placebo. The study will aim to recruit 54 participants and is planned to close to recruitment in 2017.

CMV Action

The congenital CMV parents group (http://cmvaction.org.uk/) is run on a voluntary basis by the parents of children with cCMV. The association offers very helpful advice and support to families affected by cCMV. Our research group continue to work very closely with CMV Action to develop research studies to improve prevention, treatment and management strategies and promote awareness of this poorly understood condition.

References


Seilesh Kadambini is a clinical research fellow in the Paediatric Infectious Diseases Research Group at St. George’s University of London. Seilesh’s research interests lie in the epidemiology of neonatal viral infections. Seilesh has helped coordinate congenital CMV studies in London since 2011. He has worked closely with the NHSP to prioritise integrating screening for CMV into the NHSP and improve care pathways. Seilesh was part of a collaboration that published the first evidence based guidelines to treat congenital CMV in the UK. Seilesh’s work includes laboratory studies to better understand molecular resistance patterns in cCMV infected infants treated with ganciclovir. Seilesh also works closely with Public Health England on different studies to better understand the aetiology of neonatal viral infections in the UK.

Mike Sharland is a consultant in Paediatric Infectious Diseases at St. George’s Hospital, and Professor of Paediatric Infectious Diseases at St. George’s University of London. He heads the busy Paediatric Infectious Diseases Service for South London and has a long standing research interest in congenital CMV. Mike’s research interests focus on developing and optimising antimicrobial prescribing for children. He has published over 150 papers in this area.