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The Significance and Burden of Congenital Cytomegalovirus Infection: Interviews with Two Leading Experts

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Interview Summary

Human cytomegalovirus (CMV) is a member of the family *Herpesviridae*. This virus can remain dormant in the body over a long period after initial infection. Transmission of CMV occurs through direct contact with bodily fluids, such as saliva, urine, blood, semen, and breast milk, from individuals who are actively shedding the virus in these bodily fluids. CMV is extremely common and is found throughout all geographical locations and socioeconomic groups. Congenital cytomegalovirus (cCMV) infection is the most common congenital infection globally and has potentially severe consequences for infants; however, there is little awareness of cCMV infection among pregnant females, families, and healthcare professionals (HCP).

For this article, EMJ conducted interviews in March 2023 with two leading experts: Christine E. Jones from the University of Southampton and University Hospital Southampton NHS Foundation Trust, UK; and Megan Pesch from the C.S. Mott

Children's Hospital, University of Michigan, Ann Arbor, USA, and the National CMV Foundation, Tampa, Florida, USA, both of whom have a wealth of experience and expertise in the management of cCMV. The experts gave valuable insights into topics such as the impact of cCMV infection on infants and their families and on public health; and screening, diagnosis, and treatment of cCMV infection. The experts also explored the potential complications of cCMV, particularly sensorineural hearing loss, the importance of prevention of maternal infection, and strategies to raise awareness of cCMV infection among HCPs and the public. In addition, Pesch provided a patient advocate perspective on the consequences of cCMV infection, sharing their experience of how cCMV has impacted their child, themself, and their family.

INTRODUCTION

CMV has a 230-kb double-stranded DNA genome and, like other viruses in the herpes family, once an individual has contracted a primary CMV infection, the virus establishes lifelong latency. CMV is very common; many people have had a CMV infection without knowing it, as it can be asymptomatic or manifest as mild flu-like symptoms if contracted in childhood or adulthood. However, if CMV infection occurs *in utero*, it can have significant lifelong impacts.

Global CMV seroprevalence is estimated to be 83%, with the highest rate seen in the World Health Organization (WHO) Eastern Mediterranean region (90%), and the lowest in the European region (66%).[1] Seroprevalence increases with age.[2] In the USA, approximately 30% of children who are breastfed are exposed to CMV through breastmilk,[3,4] approximately 40% of children are infected with CMV by the age of 5 years, and more than half of adults are infected by 40 years of age.[5] There are notable racial and ethnic differences in the prevalence of cCMV, even after adjusting for socioeconomic status and maternal age.[6]

Live-birth prevalence of cCMV in low- and middle-income countries (1.42%; more than one in 100 infants) is three-fold greater than in high-income countries (0.48%; approximately one in 200 infants).[7] The number of children with cCMV infection is likely to be far higher than those diagnosed as, in the absence of screening, most infections will remain undetected. cCMV infection may also be associated with miscarriage, pre-term delivery, intrauterine fetal demise, and termination of pregnancy, in cases of severe fetal abnormality on ultrasound.[8-12] The infection rates represent a huge number of infants at risk of lifelong consequences of cCMV, and the associated global public health and economic impact. Therefore, there is a need to increase awareness of cCMV among HCPs, pregnant females, and their families, including strategies to reduce maternal risk of CMV infection.

WHICH POPULATIONS ARE MOST AT RISK OF CYTOMEGALOVIRUS INFECTION?

CMV can cause a variety of clinical syndromes, depending on the age and immune status of the infected individual. In most healthy, immunocompetent individuals, CMV acquired after birth is associated with few, if any, symptoms. Primary CMV infections are predominantly associated with a flu-like syndrome with persistent fever and fatigue.[13]

Replication of CMV in the absence of an effective immune response is central to the pathogenesis of disease. Therefore, infection with the virus is an important health concern for individuals whose immune system is suppressed, such as those who have undergone solid organ, bone marrow, or stem cell transplantation, and individuals with HIV/AIDS. Those whose immune system is immature, such as fetuses, neonates, and pre-term babies are at increased risk. Primary CMV infection occurs in 1–4% of pregnancies,[13] but not all infections are transmitted to the fetus. cCMV transmission rates may be as high as 30–40%[14,15] in females who acquire primary CMV infection during pregnancy and are approximately 1%[15] in females with non-primary (latent) infection, highlighting the need for prevention of primary maternal

infection. Maternal–fetal CMV transmission rates following primary maternal infection increase as pregnancy progresses,[16] with rates of approximately 30% in the first trimester, and up to approximately 70% in the third trimester.[17,18]

IMPACT OF CONGENITAL CYTOMEGALOVIRUS INFECTION ON INFANTS, THEIR FAMILIES, AND PUBLIC HEALTH

cCMV infection is associated with lifelong consequences, including sensorineural hearing loss and neurodisability, in up to one in four children infected *in utero*.[19] Approximately 90% of infants with cCMV infection are asymptomatic at birth; however, up to 15% of these will develop long-term problems later on.[13,20] Approximately half of infants who have clinical features of CMV at birth will develop long-term sequelae.[21]

Both Jones and Pesch emphasised that the timing of cCMV infection is important in terms of adverse outcomes. Neurodevelopmental problems[22] and cases of sensorineural hearing loss[23,24] are significantly more likely to be associated with infection in the first trimester, during which there are important neurodevelopmental processes, than the second or third trimester, when the fetus is more developed.

Children who are most severely impacted by cCMV will need lifelong care, which impacts their families,[25] healthcare systems, and national economics.[26] Jones and Pesch highlighted that cCMV infection may be associated with an increased risk for epilepsy,[27] autism spectrum disorder,[27,28] and attention deficit hyperactivity disorder,[29] all of which represent a substantial public health burden.

cCMV has a significant effect on health-related quality of life of children with cCMV, their parents, and siblings.[30,31] Children whose health is moderately or severely impacted by cCMV and their parents report poorer health-related quality of life than children whose health is less severely impacted and their parents.[30] Jones stated that it is important that health economic analyses take into account health-related quality of life data to inform allocation of resources for the prevention and treatment of cCMV.[30]

A study of the annual economic burden of managing cCMV and its sequelae in the UK in 2016 showed that the total cost of cCMV is substantial (mean [range]: 732 million GBP [495–942 million GBP]), predominantly stemming from the cost of managing long-term impairments.[26]

SCREENING AND DIAGNOSIS OF CONGENITAL CYTOMEGALOVIRUS INFECTION

Screening for cCMV is not currently recommended by the UK National Screening Committee.[32] However, the committee pledged to engage with stakeholders and the National Health Service (NHS) to help improve awareness and knowledge of CMV among the public and HCPs.[32]

Pesch disclosed that the American Academy of Pediatrics (AAP) has not yet released recommendations for screening of cCMV. However, increasing numbers of healthcare systems in the USA and Canada are incorporating neonatal cCMV screening into routine care. Minnesota, USA, and a few provinces in Canada have adopted universal screening. Jones suggested that it is important for healthcare systems in other states, provinces, and countries to follow these screening programmes closely to inform decisions about future screening strategies. Pesch noted that some hospital systems are screening all babies who do not pass newborn hearing screening,[33] and/or are small or have microcephaly, but considered that "screening of every baby at birth is needed to enable us to understand the real burden of cCMV disease."

Healthcare systems in Ontario, Canada, have been screening for cCMV in newborns using the heel-prick (or dried blood spot) test since 2019 and have identified many cases of cCMV.[34] According to Pesch, this screening programme could be translatable to healthcare systems in other countries, although more sensitive screening tools, such as saliva swab tests,[33] may pick up more cases of cCMV infection in newborns.

Ultrasound signs that are suggestive of cCMV infection in fetuses include cranial (ventriculomegaly, calcifications, microcephaly,

and white matter abnormalities), extracranial (small-for-gestational age, hypoechogenic bowel, and hepatosplenomegaly), and placental (placentomegaly and calcifications) abnormalities.[35]

Most newborns with cCMV have no clinical features of infection.[20] Jones described signs of cCMV infection observable at birth, including blueberry muffin rash (indicating extramedullary erythropoiesis), petechial rash, purpura, microcephaly, prolonged jaundice, and small-for-gestational age.[36] Other, less common, abnormal neurological signs include hypotonia, hypertonia, and poor sucking reflex.[36]

Diagnosis of cCMV infection is difficult because some of these signs are non-specific and do not automatically indicate this type of infection. Jones suggested that CMV needs to be considered as a differential diagnosis for infants presenting with one or more of these features, prompting further investigations. More specific features, like brain calcifications on neuroimaging, are more likely to prompt the HCP to consider cCMV as a possible diagnosis. Diagnosis of cCMV infection can be confirmed within the first 3 weeks of life using PCR to detect viral DNA in urine, saliva, or blood, with urine being the preferred sample.[37,38]

SENSORINEURAL HEARING LOSS IN INFANTS WITH CONGENITAL CYTOMEGALOVIRUS INFECTION

Sensorineural hearing loss ranges from mild unilateral to profound bilateral hearing loss, and may be late onset, progressive, or fluctuating.[39] Infants who do not pass newborn hearing screening are referred for formal audiological testing and this should trigger testing for CMV. Some centres are instituting testing at the time of newborn hearing screening to ensure that a sample is collected and tested within 21 days of life, to confirm the diagnosis and to facilitate timely treatment where it is indicated.[33]

For those infants and children diagnosed with cCMV, routine audiology testing should continue for at least the first 6 years of life to pick up emerging sensorineural hearing loss. Jones explained that the cut-off of 6 years for this robust follow-up programme is based on cohort studies,[40] which indicate that most hearing loss occurs during early childhood.

Infants with sensorineural hearing loss may be supported with hearing aids[41] or cochlear implantation,[42,43] which is an expensive procedure. Jones considered that interventions that prevent cCMV-associated hearing loss requiring cochlear implantation are likely to be cost-effective.[44]

TREATMENT OPTIONS FOR CONGENITAL CYTOMEGALOVIRUS INFECTION

Antiviral treatment options for some infants with cCMV who have evidence of central nervous system involvement, including sensorineural hearing loss, are valganciclovir, given orally, or ganciclovir, administered intravenously, ideally soon after birth and for 6 months.[45,46] These recommendations are based on the results from randomised controlled studies.[47-49]

Antiviral treatment is currently not recommended for all infants with cCMV, and is reserved for those with more severe presentations. Pesch remarked that there have been few studies on antiviral treatment in infants with cCMV infection, and no robust studies using antivirals or other strategies on nuanced developmental outcomes. According to Pesch, the use of antiviral treatment in this population depends not only on clinical presentation, but also on geography and practice patterns. In Europe, antivirals are recommended for a wide range of clinical presentations of cCMV, and there seems to be more 'cautious prescribing' of these drugs in the USA. Jones explained that it is difficult to identify females with primary infection in pregnancy in the absence of routine antenatal screening; however, maternal treatment with valaciclovir as soon as possible after confirmed primary infection in pregnancy has been shown to reduce fetal infection by 71%.[50,51]

PREVENTION OF MATERNAL INFECTION

Jones emphasised that children with primary infection excrete CMV in their saliva and urine for prolonged periods,[52,53] and are a common source of CMV transmission to pregnant females. Females may, therefore, be at higher risk of infection during second and subsequent pregnancies compared with first pregnancies. Infants attending childcare centres are at increased risk of childhood CMV infection compared with those without exposure in childcare settings.[54] Prevention of maternal infection is essential to drive down cCMV infection rates. Strategies to reduce the burden of cCMV infection include maternal education about risk-reduction behaviours.[55]

Pesch remarked that cCMV infection rates were expected to spike during the COVID-19 pandemic as childcare centres were closed, or were open for fewer hours, and pregnant females spent more time at home with their children. However, rates were shown to be substantially reduced during the pandemic in a cross-sectional study in Minnesota.[56] Reduced childcare centre attendance and behavioural changes, such as increased hand hygiene and disinfection, aimed at reducing severe acute respiratory syndrome coronavirus 2 transmission, may have contributed to this decrease.[56] Incidental low rates of cCMV infection have also been observed in Scandinavia, which may be a result of public health campaigns to stop adults sharing food and utensils with young children to reduce the spread of *Streptococcus viridans*, which may cause dental caries.[57] Pesch commented that although these changes in infection rate were incidental and occurred in special circumstances (i.e., during a pandemic, and through a campaign for an unrelated issue), they prove that prevention can effectively reduce infection rates. Other studies that specifically incorporate CMV risk-reduction strategies have shown the potential for behavioural change to interrupt transmission and that such measures may reduce primary CMV infection.[58,59]

Jones described three simple messages that pregnant females and their families can adopt to reduce the risk of CMV infection.[60] First, share with care: try to avoid eating things that have been in a child's mouth and avoid sharing cups and cutlery; second, kiss with care: try to avoid kissing a child on the lips, and offer kisses on the forehead and cuddles instead; and third, wash with care: clean your hands with soap and water after changing a nappy or wiping a child's nose or mouth.

RAISING AWARENESS OF CONGENITAL CYTOMEGALOVIRUS INFECTION

Jones highlighted that the National Institute for Health and Care Excellence (NICE) antenatal guidelines[61] contain only one brief mention of CMV, and that there needs to be explicit inclusion of information about cCMV in antenatal guidelines. According to Jones, amending national and local guidelines to clearly state that HCPs should discuss the implications of cCMV infection with their patients as early as possible in pregnancy is necessary to stimulate effective communication. Jones considered that HCPs may be reluctant to include information on cCMV as part of antenatal education because of lack of time, unwillingness to add to patient burden and anxiety, and uncertainty about clinical pathways.[60] HCPs may also envisage an increased demand for CMV testing among pregnant females, which would be problematic as testing is not routinely offered in many locations. Creative ways to communicate about cCMV, for example, an online video with a link provided at the first antenatal (booking) appointment, are needed to minimise HCP and patient burden.

According to Jones, the majority of females of childbearing age and the wider community know little or nothing about cCMV infection,[62,63] and information "needs to be delivered in a sensitive manner that does not increase anxiety or burden, but empowers and equips females to make small and sustainable behavioural changes to reduce the risk of CMV infection, particularly in early pregnancy."

Pesch revealed that cCMV infection is not widely known or discussed by HCPs in the USA, and professional societies do not appear to prioritise the awareness and prevention of cCMV infection. For example, guidelines from the American College of Obstetricians and Gynecologists (ACOG) recommend that HCPs do not talk about CMV to their patients because prevention

strategies are burdensome and impractical for females to implement.[64] Therefore, the results of a study in Utah, USA, where only 9% of females had heard of CMV,[65] are not unexpected. Pesch observed that there is limited information on cCMV available online for HCPs or the public, and that this information has to be specifically searched for and is often hard to find. A study of the awareness of cCMV infection among HCPs in France between 2011 and 2018 showed that knowledge is improving in these professionals, but gaps remain, and HCPs are encouraged to engage in strategies, including continuing medical education, online resources, medical literature, and conferences.[66]

Jones noted that it is clear from the literature[60] and from discussions with patients that pregnant females want to receive information about cCMV to enable them to make up their own minds about behavioural changes to reduce infection risk. Furthermore, both experts remarked that the families of children with cCMV in their care often wish they had known about strategies for infection risk reduction, so that they could have made an informed choice about whether to engage in these methods. Many of these families felt uninformed, disappointed, and angry.

Jones explained that describing behavioural changes in the context of risk reduction rather than prevention makes the behaviours feel more achievable and realistic, and reduces potential feelings of failure and guilt.[60] Any information accrued by females is information for now and for the future, Jones rationalised. Females who are educated about cCMV during their first pregnancy are informed for subsequent pregnancies, and can share their knowledge with their families and other females.

Jones and Pesch advocated that conversations about cCMV become the social norm to ensure sustained changes in behaviour for risk reduction. Including cCMV risk reduction strategies in the context of well-recognised messages about health in pregnancy, such as avoiding smoking and alcohol, will help with this aim. The support of partners, as part of a wider support network, is a key factor for successful adoption of behavioural changes by pregnant females.[60,67]

PATIENT ADVOCATE PERSPECTIVE ON THE IMPACT OF CONGENITAL CYTOMEGALOVIRUS INFECTION

Pesch has a 4-year-old daughter whose health and life have been severely impacted by cCMV infection. Pesch's daughter appeared to have low-level hearing at birth, but their hearing quickly deteriorated and they were diagnosed as deaf at age 2.5 months. Cochlear implantation at approximately 12 months of age was successful for only a short while, and now they and their family are learning sign language. This limited communication is further complicated by an autism diagnosis for Pesch's daughter at approximately 2.5 years of age.

Pesch admitted that they had heard of CMV before their daughter was diagnosed with cCMV infection, but this was through a brief mention in their general paediatrics board certification training, rather than in depth during their medical school training.

Pesch described a "dual failure" in the management of cCMV infection in their experience. First, they were not informed by HCPs about the potential risks of cCMV infection and possible risk reduction strategies in pregnancy, and second, the paediatricians caring for their daughter were not informed about cCMV, and this delayed the diagnosis. Pesch felt uninformed, and that they were not given the choice to make any behavioural changes, and this led to them feeling guilty: "the 'what ifs' can never be answered."

Pesch reflected: "At the start of this journey you have no idea what your baby's future will look like [...] We felt we needed to try all options [...] It is important for families to feel they are making decisions that might change the course of their child's life rather than being passive."

cCMV infection has had a broad and significant impact on the Pesch family's life. At approximately 4 months of age, Pesch's daughter was started on antiviral therapy and was taken out of their childcare centre because of the heightened risk of immunosuppression with this treatment. Their family had to adjust and work together to cover daily care. Also, the area in which the family lived had poor services for deaf and hard-of-hearing children, so they moved to

another state and, even there, the authorities have refused to provide a sign language interpreter in class.

Pesch summarised: "Our lives were on one path, and now we are on a completely different path. The goals for our daughter's future have changed. Every aspect of life is now different." Pesch's awareness of cCMV has mostly been garnered through personal experience, rather than through professional training; hence, they believe that improving HCP awareness and knowledge about cCMV is essential.

FUTURE PROSPECTS AND CONCLUSIONS

Jones proposed that further research is urgently needed to inform decisions about antenatal and neonatal CMV screening, to assess long-term outcomes for asymptomatic and symptomatic infants, and to identify the predictors for these outcomes. Implementation research on how best to share risk-reduction measures with pregnant females and their families is crucial, particularly as there are currently no licenced CMV vaccines. Increased effort is also required to ascertain the optimal treatment for pregnant females and infants infected with CMV. In addition, clinical trials, including children with isolated sensorineural hearing loss (i.e., without concomitant central nervous system disease) are needed to improve prevention and treatment strategies in this population.

Pesch expressed that the impact of cCMV infection is underappreciated and deserves more attention and research effort. cCMV infection is associated with a spectrum of effects that deserve a spectrum of support. Universal screening; providing information on cCMV in medical training; and increasing awareness among HCPs, pregnant females, and families are important goals. Rubella used to be one of the leading causes of birth defects, including hearing loss, but is now rare as a result of widespread vaccination.[68,69] According to Pesch, cCMV is "the new rubella" and their hope is to reach the same point with cCMV as seen with rubella, with the development of an effective childhood vaccine that can be incorporated into universal immunisation programmes driving down infection rates. Pesch concluded that "this is an exciting time in cCMV research. Huge progress has been made in the last decade, with the development of screening programmes and the use of antiviral therapies, but there is still a lot of work to be done."

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