Editorial

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Universal New Born Screening for Congenital CMV Infection – Who Really Benefits?

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Editorial

The burden of congenital cytomegalovirus (cCMV) infection is high; the reported incidence is 6/1000 new borns, which is higher than the incidence of congenital hypothyroidism (0.25-0.5 per 1000), or sensorineural hearing loss (SNHL, 1.1/1000 infants) [1-3]. Just as the SNHL detected through the new born hearing screen has a range of severities, from mild unilateral loss to bilateral profound hearing loss , cCMV also has a wide spectrum of outcomes, including SNHL loss of varying severities, visual impairment, developmental delay and cognitive impairments [4]. Affected children can also remain fairly asymptomatic. cCMV infection is unique in that there is a window period beyond which the diagnosis can no longer be made. Beyond 3-4 weeks, it will not be possible to distinguish between congenital and postnatal infection, which have very different outcomes; the latter does not usually have the adverse hearing, visual or developmental sequelae. The only solution to this diagnostic dilemma in the absence of new born CMV screening is the use of polymerase chain reaction using dried blood spots taken at /soon after birth for screening of metabolic diseases, although Ross et al have shown that this method has low sensitivity and specificity for identifying cCMV [5,6].

Which children will universal screening for cCMV benefit? Cannon et al has estimated that of 25488 children with cCMV, only 3262 (12.8%) were symptomatic at birth [1]. Of these, only 815 would be diagnosed clinically as cCMV at birth (i.e. 3.2 % of all cCMV). Screening will not benefit these children. Dollard et al also showed that 12.7% of 810 cCMV infants were symptomatic [7]. Unfortunately, there is no standardised way to diagnose symptomatic cCMV at birth. Symptoms can include those related to brain involvement (microcephaly, seizures), growth (intra-uterine growth retardation [IUGR]), haematological and systemic involvement (petechia, jaundice, anaemia, splenomegaly, hepatomegaly) and respiratory involvement (pneumonia), none of which is specific to cCMV. Clinical diagnosis also depends on the number of symptoms that warrant investigation for cCMV in the different clinical settings. Dollard et al excluded IUGR, a symptom commonly found in infected infants [7]. Yet Rivera et al showed that in symptomatic cCMV infection, IUGR was an independent risk factor for congenital or late onset hearing loss [8]. Kimberlin et al considered at least one or more of a set of symptoms to define symptomatic disease for recruitment into the study on treatment of cCMV with valgancylovir [9]. The implication is that many children with non-specific or few symptoms may go undiagnosed. Cannon et al reported that 75% of children with symptomatic cCMV are not clinically diagnosed as CMV at birth and that 87.2 % of cCMV are asymptomatic at birth and hence will be missed without universal screening [1]. This editorial will focus on the impact of universal screening for cCMV on 2 major outcomes: hearing loss and developmental / cognitive problems.

Sensorineural Hearing loss

Cannon et al. showed that of the 97.8% (24673 of 25488 with cCMV) who will not be diagnosed clinically as infected, 1915 (7.5% of the whole cohort) had SNHL at birth [1]. If the main aim of screening is to diagnose SNHL, especially if CMV testing is part of the diagnostic work up of these children, screening will not benefit them. However, 2150 (8.4%) children had late-onset SNHL loss, diagnosed from 9-72 months. Lanzieri et found that by 18 years, 25% of children with cCMV had SNHL compared to 8% in controls [10]. Will new born screening benefit them?

Cannon et al. stratified children with cCMV and SNHL according to the age of diagnosis [1]. 300 children (1.8% of the cohort) who would not have been diagnosed clinically as having cCMV were diagnosed with SNHL after birth but before 9 months. As Kennedy et al. had shown that children diagnosed before this age had significantly higher receptive and expressive language scores than those diagnosed later, they concluded that these children would benefit from new born CMV screening. 256 (1%) children with hearing loss were diagnosed between 9 and 24 months [11]. Using data from the pre- new born hearing screening era, when only 18% of children were diagnosed before the age of 2 years, they concluded that SNHL would be diagnosed earlier than if CMV had remained undiagnosed and hence new born screening would also benefit this group [12]. For 1184 (4.6%) children whose diagnosis of SNHL occurred between 24 and 72 months of age, there was less evidence to show the benefit of new

born screening. So, from a cohort of 25488 children with cCMV infection, 2.8% would benefit from new born screening so that early diagnosis of postnatal SNHL could be intervened in a timely manner. Yet, it really cannot be assumed that late diagnosis of SNHL has no value. Specific intervention, hearing aids and cochlear implantation may still play useful roles in improving communication skills.

Will newborn screening be useful in identifying newborns with SNHL who would benefit from antiviral treatment? The first phase III randomised control trial of treatment with Gancylovir involved children with SNHL and CNS involvement and showed improvement in hearing outcomes at 6months with a 6 weeks course of treatment [13]. Newborn screening may not benefit this group, as the likelihood of a clinical diagnosis in the presence of CNS involvement is high. A later study by Kimberlin et al. using valganciclovir recruited infants with just one symptom at least or more, which could have been just hearing loss [9]. Although the authors clarified later that children with only SNHL without other clinical manifestation of symptomatic disease were not enrolled in large numbers, this study raises the possibility of treatment of isolated SNHL [14]. Cannon et al. had shown that 75% of symptomatic infants (2447 infants or 9.6% of the whole cohort) were not diagnosed as cCMV [1]. Thus, 1245 children who were asymptomatic but had SNHL at birth and the 2447 symptomatic but undiagnosed cCMV (14.5% of all infants with cCMV) might have benefitted from treatment, as Kimberlin et al. showed that a 6 months course improved hearing outcome at 12 and 24 months compared to a 6 weeks course [9]. This study underscores the importance of identifying cCMV in infants, now that antiviral treatment has become a possible option for an increasing number of children. Further research will be needed to bring clarity to the choice of suitable candidates for treatment.

Developmental and cognitive difficulties

Cannon et al. showed that of 815 symptomatic children diagnosed clinically to have cCMV, 763 (3% of all cCMV children) had cognitive impairment or developmental delay [1]. Screening will not benefit these children. Of 2447 symptomatic children who were not diagnosed to have cCMV, 574 (2.3%) had these difficulties. Kimberlin et al. showed that a 6 months course of treatment in symptomatic infants with at least one symptom improved the neurodevelopmental scores on the Bayley –III at 24 months, compared to a 6 weeks course [9]. Thus, screening may have benefited these children who may have been suitable for treatment. 1045 asymptomatic children (4.1%) also had these difficulties. Some of these children might have had congenital hearing loss and might have warranted antiviral treatment, if later research shows that this is useful. New born screening may then be beneficial for them.

In asymptomatic cCMV, the incidence of these difficulties is the same as in controls [15]. The possible benefit that universal screening can have for these children is based on the clinical practice of providing close developmental follow up in high risk children, which is recommended by the American Academy of Pediatrics and may also be mandated by law [16,17]. Hence, there is every likelihood that developmental problems will be identified and intervention started earlier than if they were undiagnosed. For affected children who present later with developmental delay and/or cognitive delay, the diagnostic journey might be much shorter than those without a prior diagnosis. It is unlikely that a child with cCMV who develops any of these problems will need to undergo a battery of expensive diagnostic tests. There will not be the concern of genetic problems in later pregnancies. Better prognostication is also possible with a known diagnosis. But without a structure of developmental follow up of cCMV, whether symptomatic or otherwise, the benefits of new born screening may not be so obvious for this group in infants.

Economic considerations

Cost is always an important consideration in any universal screening program. Gantt et all, with the assumption that the benefits of screening come from antiviral therapy for affected newborns to reduce hearing loss and from earlier identification of postnatal hearing loss, found that screening programs could reduce severe to profound hearing loss by 4.2 -13% with a direct cost of $10.86 per infant screened [18]. They estimated that a child with severe or profound hearing loss has a total lifetime cost of approximately US$ 1.2 million. Overall, they concluded that newborn screening for cCMV is generally associated with cost savings or is cost neutral from the perspective of net public spending and hence is warranted. In the United States, with approximately 40,000 new cases, the estimated annual cost of cCMV is in excess of 3 billion today [19].

Without ignoring the disadvantages and key ethical issues with new born screening in general, universal newborn CMV screening has significant advantages, mainly in reducing the burden of SNHL [20]. It is important to determine the usefulness of treating isolated and late onset SNHL. If this therapeutic window can be established, then universal screening will become even more important than it is today.

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