Review of screening for cytomegalovirus in the antenatal and/or the neonatal periods

Claire Townsend, November 2011

1. Introduction

Cytomegalovirus (CMV) is a common herpes virus, which is frequently acquired in early life and is usually asymptomatic. Although it only occasionally produces a mild flu-like illness in healthy individuals, more serious infection can occur in patients who are immunosuppressed. When infection is acquired for the first time in pregnancy, transmission to the fetus occurs in about 30-40% of cases. Congenital CMV can also be acquired from women with previous immunity to CMV infection (recurrent infection). The majority of infants with congenital CMV infection are asymptomatic, but around 10-15% present with CMV manifestations at birth, 40-58% of whom develop adverse outcomes, including cerebral palsy, sensorineural hearing loss (SNHL) and other neurological problems. Most asymptomatic children remain unaffected, but a small proportion develop complications, most commonly hearing impairment.

2. Rationale for this review and summary of previous review

The last review for the National Screening Committee (NSC) was carried out in 2000, with a report published in September that year (http://www.screening.nhs.uk/policydb_download.php?doc=141). The review addressed both antenatal and newborn screening for CMV: antenatal screening to detect women acquiring CMV for the first time in pregnancy, and newborn screening to identify infants with congenital infection. The review recommended that CMV screening should not be offered in pregnancy or neonatally, and the current policy not to screen was agreed by the NSC. It was also recommended that the issue should be kept under review in case of advances in diagnostics, treatment or prevention. The purpose of this policy review is to advise the NSC on whether evidence has been published since the last review that might justify a change in the current policy.
The results of the previous review are summarised briefly below:

Transmission

Transmission from mother to baby was known to occur following both primary and recurrent maternal infection but the relative risks were unclear. There was limited evidence about risk of transmission at different periods of gestation.

Natural history

Available tests were unable to identify which pregnancies would result in a congenital infection with serious sequelae, or which infected infants would be most seriously affected. Although severe complications had previously been thought to result mainly from primary maternal infections, newer studies suggested a similar risk of neurological sequelae following primary and recurrent maternal infection.

Interventions

No interventions were available to prevent or reduce the risk of transmission from mother to child, or the development of adverse outcomes in congenitally infected infants. No treatment was available for use in pregnancy. Results of a phase III clinical trial of gancyclovir in

symptomatic infants had just been published in abstract form and suggested a potential reduction in hearing deterioration in treated children, but no significant differences in mortality were reported.

Conclusion

The diagnostic pathway following screening in pregnancy was unlikely to be effective in preventing or reducing congenital CMV disease. Since the only option for women with primary infection was termination of pregnancy, it was estimated that antenatal screening could potentially result in the unnecessary abortion of substantial numbers of normally developing fetuses. Antenatal screening was therefore not considered to be appropriate.
In light of the absence of effective treatment for infected infants, screening in the neonatal period was not recommended.

3. Process of current review

A literature search was carried out in January 2011 and updated in October 2011 by Elaine Garett, Reader Services Librarian at the Royal College of Obstetricians and Gynaecologists. Publications on antenatal and neonatal CMV screening between 2003 and September/October 2011 were identified by searching Medline, Embase and the Cochrane Library.
Results were downloaded into an Access database, and 699 duplicates were removed, leaving 2430 citations (Medline 1281, Embase 1100, Cochrane 49). The titles and abstracts of these citations, and where necessary and available the full text, were examined for relevance to CMV antenatal and neonatal screening. In total, 641 citations were deemed to be potentially relevant to the topic, and were considered in this update.

4. Summary of literature since previous review

Importance of public health problem

The birth prevalence of congenital CMV in Europe is around 3 to 5 per 1000, and in the UK was estimated to be 3 per 1000 in the late 1970s. This may have changed as a result of shifts in population characteristics over the last few decades, but there are no recent estimates.
Ten to 15% of neonates with congenital infection present with CMV symptoms, which may include petechiae, hepatomegaly, splenomegaly, hepatitis, and/or neurological signs such as microcephaly, chorioretinitis and intracranial calcification. About half of these children develop permanent sequelae. A further 10-15% of those who are initially asymptomatic develop neurological manifestations, mainly SNHL, which may be bilateral, moderate or severe, or unilateral [1].
Congenital CMV is an important cause of SNHL, and accounts for 15-20% of moderate to profound permanent bilateral hearing loss [2]. However, because the onset of hearing loss can occur after the neonatal period only about half of cases would be identified through the newborn hearing screening programme. In the UK, CMV was previously estimated to account for 12% of sensorineural hearing loss, and 8% of cerebral palsy [3].
A UK study of clinically diagnosed cases of congenital CMV reported through the British Paediatric Surveillance Unit identified 86 children with confirmed congenital CMV and 70 possible cases over a 2-year period (2001-2002) (0.06 confirmed cases per 1000 births) [4]. These children are likely to represent only a small proportion of all affected children, and the true burden of congenital CMV disease in the UK is currently unknown.

Epidemiology and natural history

There are limited contemporary data on CMV seroprevalence in pregnant women in the UK, but around 40-60% are likely to be seropositive. A study in the 1980s showed that CMV immunity was more common in older, parous women, and in those who were unmarried. There were also substantial differences by socioecomonic status and ethnic group, with seroprevalence ranging from 46% in white women to 88% in Asian women [5]. Given the changing demographic profile of pregnant women in the UK, seropositivity rates may have changed in recent years.

Congenital CMV can result both from primary and recurrent maternal infection. If a woman acquires infection in pregnancy there is a 30-40% risk of transmission to the fetus [6]. The risk of reactivation or reinfection among seropositive women is unknown, although it is interesting to note that in countries where most women are seropositive, the prevalence of congenital CMV is high, at over 1% [6]. There is increasing evidence pointing to the role of reinfection in seropositive women, but its importance is unclear. It also remains uncertain whether the risk of sequelae in children with congenital CMV differs according to type of maternal infection. Primary infection was previously thought to result in more severe outcomes, but some studies have reported similar outcomes in infants whose mothers had recurrent infections. Further research is needed to clarify the risk of adverse outcomes according to type of maternal infection.

Although earlier studies suggested no differences in rates of intrauterine transmission by trimester of maternal infection, there is increasing evidence that seroconversion in late pregnancy is associated with a higher rate of congenital infection. In a study in France, the risk of transmission following seroconversion in pregnancy was 47% overall, with an increase over the course of pregnancy from 35% in the first trimester to 73% in the third trimester [7]. However, transmission later in pregnancy appears to be associated with a lower risk of damage to the fetus.

Antenatal screening

Detection of maternal and fetal infection

Antenatal screening for CMV would require an initial antibody test at booking to determine susceptibility. For women who tested negative for CMV, repeat blood tests would be required at specified intervals throughout pregnancy in order to identify seroconversions. For women who tested positive on the initial sample, a series of tests would be required to identify primary infections occurring in early pregnancy (before booking). Although there have been improvements in available tests in recent years, diagnosis would rely on the detection of IgM antibodies (which can persist for up to 12 months after primary infection), and IgG avidity testing for those who were IgM positive. Low IgG avidity indicates recent infection and high avidity past infection, but a substantial proportion of tests are indeterminate with regard to timing of infection. Thus confirmation of recent primary infection in seropositive women would be challenging. Furthermore, an antenatal screening strategy aimed at identifying seroconversions would by definition exclude women whose babies may be at risk due to recurrent maternal infection.

If maternal seroconversion is detected, diagnosis of fetal infection can be made by CMV isolation in amniotic fluid about 7 weeks after maternal infection. However, this relies on amniocentesis, and is not necessarily predictive of disease in the fetus. Several approaches for predicting the risk of adverse fetal outcome have been explored, including ultrasound of the fetus or placenta, MRI, amniocentesis and fetal blood sampling. Although some investigations can provide an indication of fetal morbidity, no single test can predict outcome in the infant.

Prevention of primary infection in pregnancy

There is some evidence to suggest that behavioural interventions to prevent primary CMV infection in pregnancy can be effective. A French study involving almost 2600 pregnant women demonstrated a significantly lower seroconversion rate after hygiene counselling was provided at around 12 weeks of gestation [8]. However, there have been no randomised trials of behavioural interventions in pregnancy. Because seropositive women may be at risk of reinfection in pregnancy, these measures could also apply to this group.

Prevention of transmission from mother to child

A recent Cochrane review published this year noted that there have been no randomised controlled trials of antenatal interventions to prevent transmission of CMV from mother to fetus [9]. There are currently no treatments for CMV infection in pregnancy: ganciclovir is contraindicated, while the use of valacyclovir has not been properly investigated. CMV hyperimmune globulin has been shown in a small study in Italy to be associated with a reduction in the risk of transmission, and is currently being investigated in two randomised controlled trials (http://clinicaltrials.gov/ct2/show/NCT01376778, http://clinicaltrials.gov/ct2/show/NCT00881517).

Because of the complexities around diagnosis of maternal and fetal CMV infection, and lack of available interventions to prevent transmission or development of congenital CMV disease, antenatal screening is not recommended at this time. The focus in recent years seems to have shifted towards neonatal screening.

Neonatal screening

Because the majority of infants with congenital CMV are either asymptomatic or exhibit non-specific manifestations, only a small proportion of infants with congenital CMV are identified through routine clinical care. Diagnosis requires collection of an appropriate sample in the first two weeks of life; after this time congenital CMV infection cannot be distinguished from postnatal acquisition, which occurs commonly through breastfeeding but does not appear to pose a risk to healthy term infants.

The most obvious platform for congenital CMV screening would be the neonatal dried blood spots (DBS), which are routinely used to screen for other conditions. However, CMV viral load in blood is significantly lower than in urine or saliva, and sensitivity of PCR tests has been reported to range from 70% to 100% [10]. Only one study has attempted universal population-based screening using a high throughput DBS PCR assay, but even the most sensitive of two methods identified only 34% of 92 infants with congenital CMV among 22500 infants [11]. Despite recent improvements in laboratory techniques for detecting CMV in dried blood spots, this approach has not yet been demonstrated to be sensitive enough for use in a large-scale newborn screening programme. However, the situation could change as DNA extraction methods and PCR assays are refined. If a sufficiently sensitive and specific test did become available, the costs and logistics of adding a PCR-based test to the newborn screening programme would require careful consideration.

Other approaches to newborn screening for congenital CMV include saliva- or urine-based testing, which are also the gold standard for congenital CMV diagnosis when carried out in the first two weeks of life. Due to the higher CMV viral loads in these samples compared with blood, better sensitivity is achieved. In a population-based screening study of almost 35000 infants in the US, 85 infants with congenital CMV were identified by testing of either a liquid or dried saliva sample, with sensitivity reported to be >97% [12]. Although the collection of saliva is relatively easy and non-invasive, the requirement for an additional sample to be taken alongside the neonatal blood spot is a potential barrier to the adoption of this approach. Screening of newborns based on urine samples is more problematic due to the

difficulty of obtaining samples, but studies based on this method have been successfully implemented in Japan [13].

Predictors of adverse outcome

Following detection of congenital CMV, infants need to be assessed to identify symptoms and check for neurological manifestations. Those with signs of central nervous system involvement have a substantial risk of developing adverse sequelae, and may benefit from treatment with gancyclovir. On the other hand, for those with transient or non-specific symptoms, or who are asymptomatic at birth (85-90%), it is not currently possible to predict whether hearing loss or other adverse outcomes will develop. Because of the risks associated with ganciclovir treatment and the lack of clinical trial data on its use in this subgroup, no intervention is currently available for these children.

Treatment and interventions for infants with congenital infection

The only recommended treatment for congenital CMV is ganciclovir. At the time of the last NSC review, preliminary results from a randomised trial of intravenous gancyclovir in newborns with symptomatic congenital CMV involving the central nervous system had just been made available. In the subsequent peer-reviewed publication, Kimberlin and colleagues reported significantly better hearing outcomes in infants treated with 6 weeks of intravenous gancyclovir, compared with untreated infants. In the treatment group, 21 of 25 (84%) infants had improved or stable hearing at 6 months, compared with 7 of 17 controls (41%, $p<0.01$) [14]. At one year, the hearing of 5 of 24 treated infants (21%) had deteriorated, compared with 13 of 19 controls (68%, $p<0.01$). Significantly lower rates of developmental delay were also reported: at one year post-treatment, treated children had significantly fewer unmet developmental milestones compared with controls (10 versus 17, $p=0.02$) [15]. However, concerns about toxicity were raised, with almost two thirds of infants experiencing neutropenia [14]. Furthermore, a high rate of loss to follow up was reported, including a disproportionate number of premature infants, raising the possibility of bias.

As ganciclovir can only be administered intravenously, the need for prolonged hospital stays precludes longer duration of treatment, particularly in the absence of clear evidence for a benefit. An oral formulation, valganciclovir, is now being investigated as an alternative or addition to intravenous ganciclovir. Observational studies have suggested improved outcomes in infants treated with 6 weeks of ganciclovir followed by 6 months of oral valganciclovir. A randomised controlled trial is currently underway to compare 6 months versus 6 weeks of oral valganciclovir in symptomatic infants with congenital CMV (regardless of the presence of neurological symptoms) (http://clinicaltrials.gov/ct2/show/NCT00466817).

For asymptomatic children, regular audiological monitoring would enable early detection of hearing loss occurring after the newborn period. Early intervention and management have been shown to improve speech and language outcomes in children with hearing impairment. Nevertheless, the majority of asymptomatic children would remain healthy, and frequent monitoring of these children could lead to increased parental anxiety.

Other research with likely implications for the prevention of congenital CMV

Vaccine development

Progress has been made towards the development of a vaccine to prevent maternal primary CMV infection. In a phase II randomised trial, 18 of 225 women who received a recombinant CMV glycoprotein B vaccine acquired infection, compared with 31 of 216 in the placebo group. Rates of infection were 3.3 per 100 person-years in the vaccine group and 6.6 in the placebo group, corresponding to an efficacy of 50% ($p=0.02$) [16]. Furthermore, this same vaccine has been shown to boost antibody and CD4+ T-cell responses in women with pre-

existing immunity [17]. Further research is needed to determine whether these responses would translate into a reduction in mother-to-child transmission among seropositive mothers.

5. Summary

- Congenital CMV can result from primary maternal infection during pregnancy, with transmission to the infant occurring more frequently following acquisition in the third trimester than earlier in pregnancy; however, the risk of adverse consequences for the infant are lower when transmission occurs later.
- Congenital CMV can also occur in infants born to seropositive women, as a result of recurrent infection. There is increasing awareness of the role of reinfection among women with pre-existing immunity, although the risk of damage to the infant is unclear.
- Maternal primary infection in pregnancy can be diagnosed using tests for IgM antibodies and IgG avidity, but these are not currently sensitive enough for screening.
- If a primary maternal infection is identified, a number of procedures ranging from ultrasound to fetal blood sampling can provide information on the risk of neurological abnormalities in the fetus. However, there is currently no consensus on the best approach, and no single test can predict outcome in the infant.
- Different strategies for newborn screening have been investigated; both neonatal dried blood spots and saliva swabs could be of potential value in the future.
- Behavioural interventions may be effective in improving hygienic practices and preventing acquisition of primary infection in pregnant women, but have not been tested under controlled conditions.
- Intravenous ganciclovir is the only recommended treatment for infants with congenital CMV, but it has only been tested in infants with neurological manifestations. Its oral formulation, valganciclovir, is currently being investigated in a clinical trial of short- versus long-term treatment in infants with any symptoms.
- A vaccine has been developed, which reduces the risk of CMV acquisition in pregnant women and may also boost immune responses in seropositive women.

6. Recommendations

It is recommended that the current policy not to screen for CMV in pregnancy or in newborns should be retained. However, this position should be reviewed periodically in light of recent advances and ongoing research, including several clinicial trials.

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