Postnatally acquired Cytomegalovirus Infection in Extremely Premature Infants – how best to manage?

Seilesh Kadambari [1] , Elizabeth Whittaker[2,3], Hermione Lyall[2]

[1] Oxford Vaccine Group, Department of Paediatrics, University of Oxford and the NIHR Oxford Biomedical Research Centre, Oxford, UK
Email: seilesh.kadambari@paediatrics.ox.ac.uk
Phone: +44 1865 226 953

[2] Department of Paediatric Infectious Diseases, St Mary's Hospital, Imperial College NHS Healthcare Trust, Praed Street, London W2 1NY, UK

[3]Department of Academic Paediatrics, Imperial College, 2nd Floor Wright-Fleming Building, Norfolk Place, London W2 1PG

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Abstract

Postnatal cytomegalovirus (pCMV) infection is a common viral infection typically occurring within the first months of life. pCMV refers to postnatal acquisition of CMV rather than postnatal manifestations of antenatal or perinatal acquired CMV. pCMV is usually asymptomatic in term infants, but can cause symptomatic disease in preterm (gestational age <32 weeks) and very low birth weight (VLBW, <1500g) infants resulting in sepsis, pneumonia, thrombocytopaenia, neutropaenia, hepatitis, colitis, and occasionally death (1,2). There are significant uncertainties regarding the management of premature infants with pCMV disease which is in part due to our limited understanding of the natural history of this disease. This review describes the current epidemiology and clinical manifestations of pCMV disease which should alert clinicians to test for CMV and also outlines a strategy to manage the condition.

Case vignette

A 47 day old ex 25/40 gestational infant presents with signs of sepsis. Blood results show thrombocytopaenia, neutropaenia and abnormal liver function tests. The baby is managed conservatively for possible necrotising enterocolitis (NEC). Of note, a screening saliva swab on D1 of life was negative for CMV DNA by PCR but CMV viraemia of 340,000 copies/ml is detected as part of an investigative screen for this episode. Should she be treated for pCMV?

Epidemiology

In the UK, preterm infants are not routinely screened for CMV infection, but a number of international cohort studies have explored the incidence of infection and disease. More than 80% of women who are seropositive for CMV will excrete the virus in breast milk (1–3). Vochem and colleagues, in one of the earliest prospective observational cohort studies, showed that 59% (17/29) of infants born at <32 weeks' gestation were CMV infected via breast milk from their seropositive mothers (3). Another early prospective epidemiological study of in preterm infants born at <32 weeks revealed a transmission rate of 37% (27/73) via breast milk (4). A systematic review, showed that symptomatic pCMV disease occurred in 0–34.5% (median 3.7%) and severe sepsis-like symptoms in 0–13.8% (median 0.7%) (1).

Little or no virus is detected in colostrum. However, CMV DNA is increasingly detected in breast milk to a maximum level at 4-8 weeks of lactation, with decline in the subsequent

weeks, often to minimal levels (5,6). CMV seropositive women also secrete virus in the birth canal, saliva and urine. Where early CMV infection occurs within the first 4-6 weeks of life, this can be acquired from birth canal or breast milk (7). Prolonged rupture of membranes may be associated with an increased risk of early transmission of CMV (8).

CMV is excreted by mammary epithelium and found in both the milk whey and cellular (leukocyte) compartments. Cell free virus in the whey has been associated with a higher transmission risk (4,5,9,10). Mothers with earlier onset of CMV excretion in breast milk, higher CMV milk viral loads and who excrete for longer, are more likely to transmit CMV to their infants (2,11,12). These studies also highlighted that low birth weight (<1500gm), prematurity (<32 weeks gestational age) and early postnatal transmission of virus were all risk factors for symptomatic disease (2,11). It has been suggested that trans-placental anti-CMV IgG may be protective in infants born after 34 weeks' gestation (2). One study found that high avidity IgG in the milk may be protective (13).

To reduce the risk of CMV transmission, breast milk may be freeze-thawed or pasteurised. Traditional pasteurisation reduces the energy, fat and lactose content of milk. It requires precision methodology and regular training of parents and healthcare professionals (14), However, short term pasteurisation (5 seconds at 62^0c) may be a viable alternative. In a prospective interventional cohort study of 87 preterm infants <32 weeks, (15) only 2 out of 87 infants (2.3%) had a pCMV transmission in the pasteurisation group, compared to 17 out of 83 (20.5%) in a historical control group.

The position of the American Academy of Paediatrics is that the benefits of fresh breast milk from seropositive mothers outweighs the risk of pCMV infection (16). However, the French Neonatal Society advises pasteurisation of breast milk from seropositive mothers for infants born at less than 28 weeks gestation (or 1000gm) until aged 31+6 weeks equivalent (17). A third of German and Austrian NICU's also give pasteurised milk to infants less than 32 weeks gestational age or 1500gm (18).

Screening for CMV Acquisition

There is no consensus on prospective diagnosis of infants with pCMV disease. A negative saliva CMV DNA PCR result at birth confirms that an infant does not have congenital infection and thus any subsequent detected infection must be postnatally acquired. Screening salivary samples CMV DNA have been shown to be highly sensitive and acceptable to parents (19,20). These should be taken before a breast feed to avoid false positive results. Serial saliva samples could potentially be tested regularly for CMV DNA using PCR in infants less than 32 weeks to enable early identification (21). However, pre-emptive screening has not been assessed for clinical or cost effectiveness and further studies of natural history and long term outcomes of pCMV infection are required to support this.

Clinical presentation

Symptomatic pCMV disease in preterm infants typically occurs in the second or third month of life. Attributing clinical disease to pCMV infection can be challenging as the presentation mimics bacterial/fungal or other viral causes and ranges from asymptomatic to life threatening multi-organ failure. The commonest manifestations of pCMV disease are highlighted below and an overview of the findings from the largest clinical cohort studies in the last two decades is presented in table 1.

Sepsis like symptoms (SLS)

The features of SLS caused by pCMV mimic bacterial sepsis and are characterised by a triad of apnoeas, bradycardias and grey pallor (1). A low threshold for testing is required. Currently, CMV testing is often only performed when there is no clinical improvement after first line antibiotic treatment.

Hepatitis

Infants with pCMV disease should be monitored for development of acute hepatitis, jaundice, hepatomegaly and cholestasis which are all recognised hepatobiliary complications (1,11). A US cohort study showed that conjugated hyperbilirubinaemia (66%; 119/180) and less commonly transaminitis (AST >150 U/L and ALT >90 U/L in 16%; 23/147) were frequently observed.

Marrow suppression

The largest published study of pCMV in preterms highlighted that thrombocytopaenia (66%; 188/283) and neutropaenia (34%; 88/261) were frequently observed as either isolated findings or in conjunction with other clinical features (22). Neutropoenia and thrombocytopaenia have also been reported to occur more commonly in 40 pCMV infected cases compared to GA matched controls (23). Preterm infants with evidence of persistent marrow suppression should always be tested for CMV.

Gastro-Intestinal

The association between pCMV infection and bowel inflammation, including necrotising enterocolitis (NEC), strictures, volvulus and colitis is well documented (24–29). Monitoring CMV viral loads in babies with NEC and ensuring that tissue resected intra-operatively is histologically evaluated for CMV is necessary to confirm pCMV mediated disease.

Pneumonitis

CMV pneumonitis is a recognised clinical feature of pCMV disease (1,2). CMV may cause lung disease through direct infection, an indirect inflammatory response, or incremental deterioration in respiratory status which contributes to prolonged mechanical ventilation. This may have longer term effects; a retrospective cohort study of 606 infants with pCMV infection revealed an increased risk of BPD (risk ratio, 1.33; 95% CI 1.19 - 1.50) (22).

Meningitis / Encephalitis

Bearing in mind the common central nervous system presentations of congenitally acquired CMV, it is interesting that postnatal CMV infection in extremely premature infants has not been shown to cause meningitis or encephalitis. However, it could be anticipated that CMV may be identified more frequently in the CSF where diagnostic multiplex PCR assays that include CMV are routinely used. The relevance of identifying CMV in the CSF should be correlated with clinical presentation.

Retinitis

Preterm infants <32 weeks/<1500gm undergo Retinopathy of Prematurity (ROP) screening as part of routine standard of care (30). Retinitis is very uncommon in children with pCMV but

may be missed if a preterm infants has been discharged from an ROP screening service before developing infection. Retinal screening should be performed in viraemic babies as it is an indication for treatment. Of note, retinal haemorrhages may be due to thrombocytopaenia rather than active CMV related retinitis so expert ophthalmological review is essential.

Hearing

Multiple population based cohort studies have shown no association between pCMV infection and sensorineural hearing loss (SNHL) (32,36,37).

Neurodevelopmental Outcome after pCMV

Recent data have demonstrated reduced occipital fractional anisotropy on cerebral diffusion tensor imaging in preterm infants compared to uninfected controls (31). However, associated adverse neurodevelopmental outcomes were not confirmed in this study. Neurodevelopmental assessment to the age of 6 years was performed in 49 infected infants, with no difference in the first 3 years of life identified. Although pCMV infected children had significantly lower verbal IQ scores at the age of 6 years, multiple regression analysis indicated no impact of CMV status but significant influence of maternal education and ethnicity (32). A single centre case controlled study on 19 CMV infected infants showed subtle, non statistically significant, differences in motor and cognitive outcomes (33). A larger, prospective controlled study of 42 infants <1500gm revealed pCMV infected infants had statistically significant lower scores in simultaneous processing scale (SIM) part of the Kaufman Assessment Battery for Children (34) when assessed from 4 years of age. A further long term follow up study of adolescents, showed that adolescents those born <1500gm with evidence of early pCMV infection through breast milk, had reduced significantly lower cognitive ability compared to preterm uninfected controls using the Weschler Intelligence Scale for Children Fourth Edition (35). Further studies are required to fully ascertain the long term effects of pCMV, and to differentiate these from the consequences of extreme prematurity.

Diagnosis

Distinguishing between congenital and postnatal infection where CMV is detected after three weeks of life is challenging. Retrospectively diagnosing cCMV relies upon isolating the the virus on the Dried Blood Spot, such as the dried blood spots collected as part of screening for congenital conditions. Diagnosis of pCMV is based on detection of CMV DNA by PCR, after day 21 of life, from blood, urine, cerebrospinal fluid (CSF), saliva (obtained at least 1 hour after breast feeding to avoid false positive results) or respiratory secretions (nasopharyngeal aspirate or bronchoalveolar lavage). Table 2 outlines the clinical, laboratory and radiological features that should prompt a clinician to consider testing for pCMV. To our knowledge there are no robust data describing any association between CMV viral load and adverse clinical outcomes in pCMV.

Treatment

Ganciclovir has been used to treat cCMV disease for over the last three decades (40). In children, the oral prodrug Valganciclovir liquid formulation (Valcyte oral syrup – 50mg/ml), has only been licenced by the FDA for the prevention of CMV disease in high risk heart or kidney transplant patients aged 4 months to 16 years old (https://www.activatethecard.com/valcyte/#). Two randomised controlled trials in neonates with congenital CMV have shown modest benefit of antiviral treatment, with ganciclovir or valganciclovir, in preventing hearing deterioration and improved neurological outcomes at 2 years of age (38,39).

There have been no randomised trials evaluating the safety and efficacy of antiviral therapy in infants with pCMV disease. To date, only case reports and small retrospective cohort studies have reported on antiviral treatment in postnatally acquired disease and the evidence for improved outcomes is limited (41). The indication for treatment of symptomatic premature infants with pCMV is to suppress active viraemia and prevent destructive end organ disease, rather than to alter the course of a chronic infection. In the absence of clinical trials data, pCMV treatment is currently based on tertiary centre experience and limited case reports and case series. Pharmacokinetic data on ganciclovir / valganciclovir in infants less than 32 weeks gestation is also limited and further studies are required to confirm appropriate dosing.

Who to treat for pCMV

Preterm infants born <32 weeks GA/<1500gm who have confirmed severe pCMV disease (Table 3). Cases should be discussed with a Paediatric Infectious Diseases Specialist.

- severe organ disease including: hepatitis, bone marrow suppression (anaemia, neutropenia, thrombocytopenia), severe gastrointestinal manifestations, pneumonitis or possibly worsening BPD.
- Sepsis like symptoms

How to treat

Oral valganciclovir is used for enterally fed infants. Intravenous ganciclovir can be used in those unable tolerate feeds. The doses of anciclovir (6mg/kg BD IV) and valganciclovir (16mg/kg BD PO) currently used, are those for infants greater than 32 weeks gestation / or greater than 1800 grams (38,39). Close monitoring for adverse events must be undertaken, and blood levels can also be measured

Monitoring and Adverse Effects

Neutropaenia occurred in 63% and 19% of cases, in the RCT's of ganciclovir and valganciclovir for cCMV respectively (38,39). At least weekly full blood counts (FBC) should obtained during treatment. If the neutrophil count drops to $<0.5 \times 10^9$/L then medication can either be omitted until the count recovers to $>0.75 \times 10^9$/L, or if very symptomatic, granulocyte-colony stimulating factor (GCSF) may be added. Liver function and creatinine clearance should also be monitored weekly. Valganciclovir and ganciclovir are renally excreted and reduced dosing is required in the event of renal failure.

Monitoring blood CMV DNA viral loads weekly during treatment is useful to assess for antiviral efficacy. Full viral suppression usually leads to disease resolution but timing depends on the initial level of viraemia and the severity of end organ disease.

How long to treat

In our experience, a clinically pragmatic approach has been to initiate antiviral treatment for two weekly blocks, and ideally this should be with support from Paediatric Infectious

Diseases. CMV viral load (VL) should be tested weekly. If symptoms persist, and CMV VL is not fully suppressed then treatment may continue for another block. A treatment duration of greater than 8 weeks is unusual. Studies in congenitally infected infants and solid organ transplant recipient have shown that resistance to CMV has not been reported in cases who receive treatment for less than 8 weeks (42,43).

Where symptomatic disease does not respond to treatment, an underlying immune deficiency should always be considered including HIV infection or a primary severe combined immunodeficiency. Before starting ganciclovir or valganciclovir, parents should be informed of the short and long term side effects, including the potential risk of carcinogenicity and germ line damage, to date only demonstrated in animal studies.

Conclusion

Postnatal CMV disease may cause symptomatic end organ disease and / or sepsis like symptoms in around 5% of extremely premature infants and the usual source of infection is breast milk. Symptomatic disease may be effectively treated with valganciclovir / ganciclovir, but there is still insufficient data on dosing, treatment duration and side effects. Each case must be taken on its own merits, but if there are severe symptoms, we recommend treatment of post natal CMV in preterm infants, as we certainly would for the case of the infant described in the introductory clinical vignette.

Competing Interest: None declared.

	Gunkel J et al, The Netherlands (n=74)(32)	**Goelz et al, Germany (n=42)** (44)	**Hamprecht K et al, Germany (n=33)** (4)	**Josephson C et al, USA (n=29)** (8)	**Martins-Celini et al, Brazil (n=24)** (2)	**Kelly M et al, USA (n=328)**(22)
Study design	Prospective single centre observational cohort study screening infants <32 weeks GA	Prospective single centre case controlled observational cohort study screening infants <32 weeks GA	Prospective single centre unmatched observational cohort study screening infants <32 weeks GA/<1500gm birthweight	Prospective multicentre birth cohort <1500gm to three NICU's	Prospective cohort study enrolling neonates <30 weeks in two NICU's	Propensity matched retrospective multicentre cohort study
Demographics	Mean GA 28.2 weeks, 56% male, 100% breast fed	Mean GA 28 weeks, mean birthweight 1136gm	Median GA 29 weeks, median birthweight 1100 gm	Mean GA 27 weeks, 48% male, 100% breast fed	Mean GA 26 weeks, 46% male	Median GA 25 weeks, 54% male,
Main clinical features at presentation	Pneumonias (3%), SLS with pneumonia and thromobocytopaenia (1%)		Sepsis like symptoms (25%), myoclonia (12%)	NEC resulting in death (10%), SLS (3%)	Bronchopulmonary dysplasia (75%), ROP (70%), periventricular haemorrhage (45%), SLS (12%)	Bronchopulmonary dysplasia (71%), SLS (18%), NEC (4%)
Major laboratory abnormalities at presentation	Thrombocytopaenia (1%)	Not recorded	Neutropaenia (88%), thrombocytopaenia (12%),	Thrombocytopaenia and neutropenia (3%), hyperbilirubinemia (3%)	Elevated Gamma GT (50%), thrombocytopaenia (36%), neutropaenia (18%)	Thrombocytopaenia (66%), hyperbilirubinaemia (66%), neutropanenia (34%), transaminitis (16%)

Significant radiological abnormalities at presentation	LSV at TEA (36%), germinolytic cysts at TEA (15%)	Not recorded	Not recorded	Not recorded	Not recorded	Not recorded
Long term Clinical outcomes	Reduced verbal IQ at 6 years. Normal Griffiths Mental Development Scales (GMDS) months and Bayley Scales of Infant and Toddler Development, Third edition between 24 – 30 months	Significantly lower results in simultaneous processing scale of Kaufman Assessment Battery for Children (p=0.029)	Not recorded	Not recorded	Not recorded	Not recorded

Table 1: Largest cohort studies of postnatal CMV conducted since 2000

Risk factors	• <32 weeks gestation • <1500gm birthweight • Exposed to breast milk from a CMV-seropositive mother
Clinical features	• Sepsis like symptoms • Respiratory distress • Hepatomegaly • Splenomegaly • Cholestatic jaundice • NEC • BPD
Abnormal laboratory markers	• Thrombocytopaenia (<100 x10^9/μl) • Neutropenia (<0.5/mm^3) • Raised liver enzymes (AST >150 U/L, ALT >90 U/L, Gamma GT >200 IU/L) • Conjugated hyperbilirubinaemia
Imaging	• CXR: evidence of pneumonitis • CrUSS: Lenticulostriatal Vasculopathy, germinolytic cysts, • Findings consistent with NEC

Table 2: Table of clinical presentations to trigger testing for pCMV

Diagnosis:

Severe symptomatic end organ disease

AND

Positive CMV result after 21 days of life (and negative CMV screening result at birth / before 21 days of life)

↓

Antiviral treatment:

Valganciclovir 16mg/kg BD PO if tolerating enteral feeds

OR

Ganciclovir 6mg/kg BD IV, if unable to feed orally

↓

Monitoring whilst on antiviral treatment:

FBC, U&E, LFT's weekly

Blood CMV DNA Viral load weekly

↓

Treat beyond two weeks if symptoms persist and blood CMV VL not fully suppressed. Any further treatment should be with further two week courses of antivirals

Review every two weeks and rarely treat pCMV for more than 4 – 8 weeks

Table 3: Algorithm to manage postnatal CMV disease in the premature neonate

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