Early Human Development 87 (2011) 723–728

Contents lists available at SciVerse ScienceDirect

Early Human Development

journal homepage: www.elsevier.com/locate/earlhumdev

Evidence based management guidelines for the detection and treatment of congenital CMV

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ARTICLE INFO

Keywords:
Congenital
Cytomegalovirus
Diagnosis
Treatment

ABSTRACT

CMV is the most common congenital infection in newborns worldwide. Congenital CMV causes sensorineural hearing loss in a significant proportion of infected newborns, while the majority of newborns are asymptomatic. In the last three years there have been significant advances in the diagnosis and treatment of congenital CMV. We have developed practical evidence based guidelines for the management of congenital CMV.

1. Introduction

Congenital CMV (cCMV) is the leading non-genetic cause of sensorineural hearing loss [1,2]. Worldwide, the birth prevalence of cCMV is estimated at 7 per 1000 [2]. Approximately 12.7% of infected newborns are symptomatic at birth [2]. Around 13.5% of infants who are asymptomatic then develop sequelae including sensorineural hearing loss (SNHL) in childhood [2]. An accurate diagnosis has to be made within the first three weeks of life as virological and serological tests taken after this time no longer clearly distinguish between congenital and acquired infection.

Vertical transmission of CMV infection can occur through three main routes: (i) intrauterine; (ii) intrapartum and (iii) post-natal. Intrauterine transmission is the most important route as it may result in major neurological sequelae. Primary maternal infection, maternal reinfection with a different viral strain or reactivation of latent maternal infection can all cause in utero transmission. The most common source of virus for pregnant women is from young children [3]. Postpartum acquisition is mainly through breast milk. One study found infants who breast feed from seropositive mothers have an estimated rate of infection of up to 38% [4].

Congenital CMV is an important illness that is a common cause of hearing loss in newborns and a major cause of disability in children. The annual costs of CMV disease to the US health care system were estimated in the 1990's to be 1.86 billion dollars [5]. There is currently no universal screening programme for CMV but there is interest in the feasibility of linking screening for cCMV to the Newborn Hearing Screening Programme [6]. This report will discuss recent advances in detection and treatment and propose pragmatic management guidelines for congenital CMV. There is a very limited evidence base to guide the management of cCMV. We therefore conducted a systematic and comprehensive literature review using MEDLINE (1990 to May 2011) and EMBASE (1990 to May 2011) using the following terms as the Medical Subject Heading (MeSH) and text words: neonate, infant, cytomegalovirus, CMV, antiviral agents, valganciclovir, ganciclovir, management and treatment. Standard levels of evidence and grades of recommendations are used (Table 1).

2. Making the diagnosis

2.1. Clinical features

2.1.1. Symptomatic congenital CMV infection

The typical physical signs of symptomatic disease include blueberry muffin rash, petechiae, IUGR, microcephaly, hepatosplenomegaly and jaundice. Laboratory results are consistent with hepatic

Abbreviations: CNS, Central nervous system; CMV, Cytomegalovirus; CrUSS, Cranial Ultrasound; DBS, Dried blood spot; FBC, Full blood count; IUGR, Intrauterine growth restriction; LFT, Liver Function Test; MRI, Magnetic Resonance Imaging; PCR, Polymerase Chain Reaction; SNHL, Sensorineural hearing loss.

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doi:10.1016/j.earlhumdev.2011.08.021

Table 1
Levels of evidence and recommendations.

Study design	Evidence level	Recommendation grade
Good recent systematic review	Ia	A+
One or more vigorous studies	Ib	A−
One or more prospective studies	II	B+
One or more retrospective studies	III	B−
Formal combination of expert opinion	IVa	C
Informal expert opinion	IVb	D

Table 2
Summary of key recommendations for the management of congenital CMV.

	Recommendation grade
Who to treat	
1. CNS disease – SNHL, cerebral disease, chorioretinitis	B+ [15]
2. Severe focal organ disease – severe hepatitis, severe anaemia, neutopaenia, throbocytopaenia, colitis, pneumonitis	D
When to treat	B+ [15]
Start treatment within the first 28 days of life	
What to treat with	
Ganciclovir 6 mg/kg IV BD	B+ [15]
Valganciclovir 16 mg/kg PO BD when clinically appropriate	B+ [18]
How long to treat	B+ [15]
Total duration of treatment 6 weeks	
Monitoring during treatment	B+ [18]
Weekly FBC, U&E, LFT's	
Neutrophil count drops $<0.5\times10^9$/L stop medication till count reaches $>0.75\times10^9$/L	
Platelet count drops to $<50\times10^9$/L stop medication till count reaches $>50\times10^9$/L	
Creatinine clearance between 10 and 19 ml/mim/1.73 m^2 should lead to once daily dosing until creatinine clearance returns to above 20 ml/mim/1.73 m^2	

and reticuloendothelial involvement. Findings include conjugated hyperbilirubinaemia, thrombocytopaenia and elevated hepatic transaminases in the majority of symptomatic newborns [7]. Long term studies have shown that almost half of symptomatic newborns will develop SNHL, learning difficulties and microcephaly and, rarely, visual loss [7].

2.1.2. Asymptomatic congenital CMV infection

Congenital CMV is most commonly asymptomatic. Approximately 10% of asymptomatic children will develop SNHL over the first 5–7 years of life, whilst the incidence of hearing loss in the general population is only 0.1–0.4% [1]. Hearing loss can be bilateral, and is often progressive or with delayed onset therefore requiring prolonged audiological follow up [1]. Because hearing is often normal at birth, only 50% of cases of SNHL caused by CMV are expected to be detected by neonatal hearing screening programmes [1].

2.2. Laboratory confirmation of infection

2.2.1. Urine vs saliva CMV PCR

Polymerase chain reaction (PCR) amplification of viral DNA is rapidly replacing viral culture as the most sensitive and efficient method for the detection of CMV. Detection of CMV in the urine or saliva is relatively easy because newborns shed high levels of the virus from these fluids and both are amenable to rapid testing using PCR [8]. The gold standard for the diagnosis of cCMV infection in newborns has been isolation of the virus in the urine within the first three weeks of life. Collection of urine from newborns is however difficult, time consuming and not an easy method for routine diagnosis. For example, technical difficulties prevented one third of urine samples from being analysed in a comparison study assessing the diagnostic accuracy between saliva and urine PCR, whilst saliva samples were more easily obtained [8]. The authors concluded that saliva samples are as reliable and more convenient in the diagnosis of cCMV.

The most recent study on diagnosing cCMV found that real time PCR of both liquid and dried saliva showed very high rates of specificity and sensitivity [9]. This prospective multicentre study found 177 out of the 34, 989 infants recruited to be positive for CMV. The liquid saliva PCR assay detected 85 out of 17,662 infants (0.5%; 95% CI, 0.4 to 0.6) positive for CMV on both culture and PCR assay. The dried saliva PCR assay detected 74 out of 17,327 (0.4%; 95% CI, 0.3 to 0.5) positive for CMV and 76 were CMV positive on rapid culture. Real time PCR assays of both liquid and dried saliva samples had sensitivities of >97% and 99.9% respectively compared with saliva rapid culture. False positive results can cause considerable anxiety for parents but the frequency of false positive results of both liquid and dried saliva was less than 0.03%. Saliva was shown to be more sensitive in diagnosing cCMV than the use of Dried Blood Spots.

Obtaining saliva samples is easy, practical and they can be readily stored and transported to the laboratory. The high sensitivity and specificity of dried saliva PCR make this method of testing a readily applicable approach to accurately diagnose cCMV. Saliva specimens are also potentially a simple method to use in any future newborn screening programmes [10]. The most recent advances in detection of CMV have therefore demonstrated that saliva PCR is highly sensitive and specific and should now be considered as the investigation of choice to detect cCMV.

2.2.2. Problems with testing Dried Blood Spots (DBS)

The detection of CMV DNA on DBS using PCR has enabled the retrospective diagnosis of cCMV in older children who present with compatible clinical features such as SNHL. The most recent studies however have unfortunately produced inconclusive findings on whether CMV DNA PCR on DBS would accurately identify the majority of newborns with cCMV. The four largest published studies now report sensitivities ranging from 34% to 100% for the detection of CMV PCR on DBS as a confirmatory test for cCMV. The size of DBS used, differences in DNA extraction methods and PCR assay protocols as well as variations in populations tested could account for the wide range of sensitivities noted in these studies.

A recent large prospective study assessed the diagnostic accuracy of DBS PCR as a universal screening tool [8]. Infants born at seven hospitals across the U.S were recruited between March 2007 and May 2008. Saliva specimens tested by rapid culture for detection of early antigen fluorescent foci were compared with a single primer and a two primer DBS PCR. Ninety two out of 20,448 newborns had confirmed cCMV infection (0.45%; 95% CI 0.36 to 0.55), 91 of whom had positive antigen detection on saliva. The single primer DBS PCR detected 17 out of 60 (28%) infants with confirmed cCMV of the 11,422 infants screened. However, the two primer DBS PCR assay identified 11 out of 32 infants (34%) of the 9026 newborns screened. The authors concluded that DBS PCR has low sensitivity for accurate diagnosis of cCMV because approximately two-thirds of infections were missed using this method. The sensitivities for detecting cCMV on DBS PCR were much lower than in other studies. In summary, a positive DBS CMV PCR taken in the first 3 weeks of life confirms the diagnosis of cCMV,