Clinical Outcome of Cytomegalovirus Infection on Low Birth Weight Infants

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Abstract

Cytomegalovirus (CMV) is a DNA virus and a marker of the herpes virus groups, was found only in human and the infection occurs for a long time. The transmission of CMV infection to fetus/neonates is via congenital infections or perinatal infections. Clinical manifestation of symptomatic CMV infection of the fetus has early and second early manifestations. Diagnosis of neonatal CMV infection may be done by serologic test based on detection of IgM of CMV infection. The objective of this study is to asses clinical outcome of CMV infection of low birth weight infants delivery with long term sequelae. An observational study was conducted since March 2010 until December 2011 in Advent and Hermina Pasteur Hospital, all subjects were low birth weight infants (LBWI). The inclusion criterias were all LBWI delivered in those hospital or were a referred neonates. The exclusion criterias were major congenital defect, which is not related to congenital CMV infection and neonates' death before one week of life. Every neonate was examine both their physical and peripher blood count, glucose, Ca. Liver function test done for acute hepatitis and titre IgG and IgM CMV serial, head ultrasound serial and head CT scan/MRI used for babies with intracranial bleeding and hydrocephaly. There were 50 cases of LBWI, consisted of 41 preterm babies, and 30 small for gestational age babies. Clinical manifestation of acute hepatitis were found in 20% subjects, all of them with the elevation of liver function test. Microcephaly which occured in the first untill three weeks of life were 8%. Ventricular dilatation were 10% in the first week of life and increased up to 48% after three weeks. Cases with intracranial haemorrhage were found in 6% and 10% with cerebral calcification on head while sensorineural hearing loss were 8%. All of LBWI have 100% serorespon immune IgG. IgM CMV reactive only in 12% cases but after 3 weeks increased up to 32%. During neonatal up to infancy period, the prevalence of CMV infection in Bandung is high with long term sequelae which are serious and can be fatal. It is urgent and important to give information about this disease to new couples, every mother and healthcare providers in fetomaternal fields to prevent CMV infection.

Key words: CMV infection, long term sequelae, outcome

Keluaran Klinis Infeksi *Cytomegalovirus* pada Bayi Berat Lahir Rendah

Abstrak

Cytomegalovirus (CMV) adalah virus DNA dan termasuk kelompok virus herpes. Virus ini hanya menyerang manusia dan infeksinya berlangsung lama. Penularan CMV pada janin/neonatus dapat melalui infeksi kongenital atau infeksi perinatal. Manifestasi Infeksi CMV pada janin terdiri atas manifestasi awal dan lanjut. Diagnosis infeksi CMV neonatal dengan deteksi IgM CMV. Tujuan penelitian ini untuk menilai keluaran klinis infeksi CMV pada bayi berat lahir rendah dengan gejala sisa. Penelitian observasional periode Maret 2010–Desember 2011 di RS Advent dan RS Hermina Pasteur pada semua bayi berat lahir rendah (BBLR). Kriteria inklusi: semua BBLR yang lahir di kedua RS maupun merupakan pasien rujukan. Kriteria eksklusi: kelainan kongenital mayor yang tidak berhubungan dengan infeksi CMV kongenital dan bayi yang meninggal dalam minggu pertama. Setiap bayi dilakukan pemeriksaan fisis, hitung darah tepi, kadar glukosa dan kalsium, uji fungsi hati dilakukan pada bayi yang menderita hepatitis akut, pemeriksaan kadar IgG dan IgM CMV serial, USG kepala dan CT-*scan*/MRI kepala pada kasus hidrosefalus dan perdarahan intrakranial. Terdapat 50 kasus BBLR terdiri atas 41 bayi prematur, 30 bayi kecil masa kehamilan. Hepatitis akut ditemukan 20% semuanya disertai peningkatan uji fungsi hati. Mikrosefali yang terjadi sampai usia 3 minggu sebanyak 8%. Dilatasi ventrikular lateralis sebesar 10% pada minggu pertama dan meningkat sebanyak 48% setelah 3 minggu. Perdarahan intrakranial sebanyak 6% dan kalsifikasi serebral 10%. Gangguan pendengaran sebanyak 8%. IgG (+) pada semua BBLR (100%). IgM CMV reaktif hanya 12% tetapi meningkat sebesar 32% setelah usia 3 minggu. Simpulan, prevalensi infeksi CMV di Bandung cukup tinggi dengan gejala sisa neurologis yang berat dan fatal selama 6 bulan postnatal, sehingga perlu diberikan informasi mengenai penyakit ini kepada pasangan baru, setiap ibu, dan petugas kesehatan di bidang fetomaternal untuk mencegah infeksi ini.

Kata kunci: Gejala sisa jangka panjang, infeksi CMV, keluaran

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Introduction

Cytomegalovirus (CMV) is a DNA virus and a marker of the herpes virus groups.[1] This virus was found only in humans[2] and the infection occur for a long time. CMV who infected cells has abundant cytoplasm and both intranuclear and cytoplasmic inclusions. They do not resulted in rapid cell death. It is present in saliva, urine, genital secretions, breast milk and blood or blood products of infected person and can be transmitted by exposure to any of those sources.[1,2]

Risk factors of CMV infection in neonates are associated with nonwhite race, lower socioeconomic status, drug abuse and neonatal intensive care unit admittance. Premature infants are more often affected than full-term infants, it can be transmistted through transfusion with unscrened blood.[1]

The transmission CMV infection to fetus/ neonates is via congenital infections or perinatal infections.[1,2,3] Congenital infections transmitted to the fetus during in utero. The second is perinatal infections, which happens intrapartum or in the postpartum period. Maternal CMV infection is the origin of congenital infections and most perinatal infections is important to review as vertical transmission. The vertical transmission implies transmission from mother to infant. Vertical transmission can occur at anytime during gestation or in the perinatal period and usually asymptomatic especially for seropositive women before pregnancy. However, there are reports that as many as 17% of all infants with asymptomatic CMV are born from women with prior seropositivity.[2–7]

Perinatal infection of CMV may occur from intrapartum exposure to the virus in the maternal genital tract, from postnatal exposure to infected breast milk, from exposure to infected blood or blood products and nosocomial through urine or saliva. The incubation period varies from 4 to 12 weeks of exposure.[2]

There is no data about the incidence of CMV infection in developing countries such as Indonesia. In developed countries such as United States, CMV infection is the most common cause of congenital infection and occurs in 0,2 – 2,2% of all live births. They resulted in 40.000 new cases in the United States per year.[1,6]

Clinical manifestation of symptomatic CMV infection of the fetus has two presentations[1,2]

Early manifestations can include a pattern consistent with an acute fulminant infection involving multiple organ system and carrier with a higher risk of mortality up to 30%. Finding in this presentation include petechiae or purpura (79%), hepatosplenomegaly (74%), jaundice (63%) and prematurity. Laboratory abnormalities include elevated hepatic transaminase and bilirubin level. Approximately one-third were preterm and one-third have intrauterine growth retardation (IUGR).[7-9]

Second early manifestations includes IUGR and microcephaly (48%) with or without intracranial calcifications. The calcifications may occur anywhere in the brain, in the periventricular area. Other neuroimaging and central nervous system manifestation can include ventricular dilatations, cortical atrophy, migrational disorder such as lissen cephaly and pachygyria and demyelination as well as chorioretinitis in approximately 10 to 15% infants. Babies with CNS abnormalities almost always have developmental abnormality and neurologic dysfunction with intelligence quotient (IQ) score below 50, motor abnormalities, deafness and visual problem to mild learning and language disabilities or mild learning loss or sensorineural hearing loss (SNHL).[7-11]

Diagnosis of neonatal CMV infection are as follows:[1,12,13] 1) The gold standard for the diagnosis of congenital CMV is urine or saliva culture obtained before 3 weeks of age. Most urine specimen from infants with congenital CMV is positive within 48–72 hours especially if shell vial tissue culture techniques are used; 2) Polymerase chain reaction (PCR) for CMV DNA is as sensitive as urine culture for determination of CMV infection. PCR has been used successfully in retrospective diagnose of congenital CMV beyond 3 weeks of age through CMV DNA analyses of dried blood spots (Guthric cards); 3)Serologic test based on detection of IgM of CMV infection; 4) Other laboratory tests that are indicated in the work up include complete blood count, LFT, DIC panel, radiologic studies as skull film, head USG and CT-scan.

The aim of this study is to asses the clinical outcome of CMV infection in low birth weight infants delivery with long term sequelae.

Methods

An observational study was conducted since March 2010 to December 2011 in two hospitals (Advent Hospital and Hermina Pasteur

Table 1 Characteristic of Subjects

Characteristics	n=50
Sex	
Male	27 (54%)
Female	23 (46%)
Birth weight <2,500 g (range: 870–2,460 g (1,725.42)	50 (100%)
Body length (cm)	26–47 (40.78)
Head circumference (cm)	21–35 (30.75)
Gestational age	
Preterm	41 (82%)
Full term	9 (18%)
Intrauterine growth	
SGA	30 (60%)
AGA	20 (40%)
LGA	0

Hospital). All subjects were low birth weight infant who admitted in neonatal intensive care unit from Advent Hospital and Hermina Pasteur Hospital.

The inclusion criteria are all low birth weight infants with weight at birth less than 2,500 grams, with mild, moderate and severe conditions. They delivered in the two hospitals or were the referred neonates during this period. The exclusion criteria are major congenital defect, which is not related with congenital CMV infection and neonates death before one week of life, and subjects parents declined to be studied.

Physical examination including anthropometric masurements (body/birth weight, length, head circumference), gestational age, intrauterine growth, vital sign, sex and physical health was done to all subjects. Laboratory examination are peripher blood count, glucose, calcium, liver function test if clinical pattern showed jaundice and hepatosplenomegaly and IgG and IgM CMV serial at birth and every two weeks. Head ultrasound serial performed at birth and every 1-2 weeks up to 6 months of life. The criteria of immunologic responses are IgG CMV reactive ≥6 and non reactive <6, IgM CMV reactive ≥

Table 2 Morbidity of Subjects

Morbidity	n = 50 (%)
Low birth weight infant	50 (100)
Preterm babies	41 (82)
SGA	30 (60)
Hepatitis	10 (20)
Microcephaly	4 (8)
Hydrocephalus	
First week	5 (10)
Three weeks	24 (48)
SNHL	4 (8)
Cerebral calcifications	5 (10)
Intracranial haemorrhage (SDH, IVH)	3 (6)
AGA	20 (40)
LGA	0

Table 3 Laboratory Results

Laboratory Results	n = 50
Liver function test: elevated	10 (20%)
TB	8.48–13.26 (10.87)
DB	5.15–8.67 (6.91)
SGOT	116–374 (245.0)
SGPT	95 –217 (156.0)
Alkali phosphatase	348–521 (434.5)
IgG at birth	
Reactive	50 (100%)
Non reactive	0
IgG 2–3 weeks of life	
Reactive	50 (100%)
Non reactive	0
IgM at birth	
Reactive	6 (12%)
Non reactive	44 (88%)
IgM 2–3 weeks of life	
Reactive	16 (32%)
Non reactive	34 (68%)

1.0 and non reactive <0.7 and Gray score is 0.7–<1.0. Data was analyzed with SPSS 14 for Windows.

Results

Table above showed all subjects had low birth weight with mostly born preterm. The median birth weight was 1,725.42 g and head circumference 30.75 cm. All subjects had low birth weight with mostly preterm babies. The majority of subjects with hydrocephalus can be seen after three weeks being born. According of seroresponse immune of IgG and IgM CMV, all cases of low birth weight infants in this study had IgG CMV reactive 100%. Titer of IgM reactive only in 6 cases (12%). Only after 2–3 weeks of life, titer of IgM were elevated to positive reaction in 16 cases (32%) with clinical manifestation as acute hepatitis, microcephaly, ventricular dilatation/hydrocephalus, and intracranial haemorrhage as subdural haemorrhage, subarachnoid or intraventricular haemorrhage.

Discussion

In this study all subjects had low birth weight infants and mostly were preterm babies (82%). Majority had intrauterine growth retardation or small for gestational age (60%).[1,2,8,14] Classic CMV infection disease occurs in 10–15% of the cases and consists of intrauterine growth retardation, hepatosplenomegaly with jaundice, abnormal liver function tests, thrombocytopenia with or without purpura and severe central nervous system disease.[5,10,11,15] This study was similar with other that showed acute symptomatic disease not only found in preterm delivery and intrauterine retardation. Other symptoms occured are neonatal jaundice, hepatosplenomegaly (20%) with elevation of liver function tests.

Sandrak et al.[2] reported that there were 5 to 10% subjects who may have developmental abnormality, these include hearing loss, mental retardation, motor spasticity and microcephaly. This results is similar with this study which found 8% of babies had sensorineural hearing loss, 8% microcephaly and 10% cerebral calcification. Other study suggested that sensorineural hearing loss is the most common of CMV infection with 60% were symptomatic and 5% found in asymtomatic infants. Infants failing the newborn hearing screening should be assessed for CMV infection as soon as possible.

Infants with CMV infection should have hearing tested as neonates and young infants.[5,11]

The finding also showed that central nervous system complication related with ventricular dilatation or hydrocephalus was high. In the first week of life there were 10% of ventricular dilatation or ventriculomegaly, and after three weeks it increased to 48%. Some of them have received VP-shunts. The prevalence of ventricular dilatation in this study at first week and 3 weeks of life were 10% and 48% respectivelly.

The titer of IgM CMV at birth were 12% but after three weeks were increased up to 32%. There was relation among congenital CMV infection with perinatal infection from mother to infants, means vertical transmission is present. Vertical transmission can occur any time during gestation or in the perinatal period.[2,4-7] The other problem is central nervous system complication happened not only with ventricular dilatation but also with subdural and subarachnoid haemorrhage. All subjects with this complication has had head operation. All cases with acute hepatitis and ventricular dilatation with or without intracranial haemorrhage have received CMV treatment (Gancyclovir® and Valgancyclovir® drugs).[16,17]

The conclusion of this study is in Bandung, the prevalence of CMV infection during neonatal and infancy period is high with serious and long term sequelae. It is very important to provide and diseminate information about this disease to every mothers and health providers during fetomaternal care in Indonesia.

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