CASE REPORT

Multiple Complications of Congenital Cytomegalovirus Infections

Retayasa, Hamid A, Kari K

(Department of Child Health Medical School of Udayana University, Sanglah General Hospital

ABSTRACT Congenital cytomegalovirus (CMV) is the most frequently occurring viral infection of the newborn infants. Cytomegalovirus agent which commonly invades human early in life may cause a spectrum of clinical manifestations from asymptomatic to severe congenitally infected newborn with multiorgan involvement. We report two cases of multiple complications of congenital cytomegalovirus infections admitted to the Department of Child Health Sanglah General Hospital. The diagnosis of congenital CMV infections was based on clinical and laboratory examinations. The manifestations of congenital infections in the first case of a 5,5 month old Balinese girl were microcephaly, ventricular septal defect, auricular dysgenesis and rectovaginal fistula. The results of laboratory examination showed positive IgG anti CMV. The IgM anti CMV was absent. In the second case the manifestations were epilepsy, microcephaly, cerebral palsy with craniosynostosis and porencephaly. Laboratory examinations showed positive IgG anti CMV but negative IgM anti CMV. The IgM and IgG anti rubella, toxoplasma, and HSV2 were negative in both cases. **[Paediatr Indones 1997; 37:37-44]**

Introduction

Cytomegalovirus infection of the fetus and newborn can be generally be divided into three mayor categories. The first is congenital infection, this consists of infections that are transmitted to the fetus *in utero*. The second is perinatal infection and consists of infections that are acquired intrapartum or in the immediate postpartum period. The third is postnatal infection from ingestion of infected breast milk or iatrogenic as result of blood transfusion.[1,2]

Accepted for publication: November 23, 1996. Author's address: Dr. Retayasa, Department of Child Health, Medical School, Udayana University - Sanglah Hospital, Bali.

Congenital cytomegalovirus (CMV) is the most frequently occurring viral infection of the newborn infants. The incidence is 0.5-2.4% of all live birth in the United States.[3-5] CMV infection agent which commonly invades human early in life, creates spectrum of clinical involvement from the more common asymptomatic chronic excretion to the uncommon severe congenitally infected newborn with multiorgan involvement.[4] The most common findings of congenital CMV infection are petechie (79%), jaundice (63%), microcephaly (50%), chorioretinitis (12%), prematurity (34%), inguinal hernia (26%), and dental defect.[2] Ten percent of the infected neonates are asymptomatic at birth.[5] Although the majority of infants with this infection are asymptomatic at birth, but this known to result in later neurologic and audiologic sequelae such as mental retardation, hearing disability, motor abnormalities and visual disturbances.[2,3,5-7] We report two cases of multiple complications of congenital CMV infections admitted to Department of Child Health Sanglah General Hospital Denpasar.

Case 1

A 5 1/2-month old Balinese girl was admitted to Department of Child Health Sanglah General Hospital Denpasar on February 21, 1997 with the main complaint of seizures. The seizures occurred twice a day with an interval of 5 hours. The characteristics of seizures were generalized tonic clonic for approximately 5 minutes. She never had loss of consciousness or neurological deficit after the seizures. She never had any seizure previously. She had fever and cough three days before the seizure developed. He has had colostomy for a rectovaginal fistula when she was 2.5 months old. She was born spontaneously at term with the body weight of 3000 grams. Her mother denied any serious illness when she was pregnant.

On physical examination the girl was well-nourised; she was in a good condition and alert. The body weight was 6 kg; the respiratory rate was 54/minute, shallow and regular. The pulse rate was 146 beats/minute, regular. The body temperature was 36.5°C. The head circumference was 37 cm (< 2SD below the Nellhaus standard). The fontanel was closed already. There was no strabismus, deviation conjugee or cataract in the both eyes. The throat was inflamed. There was no stiffness of the neck. There was a dysgenesis of the right auricle. The chest was symmetrical. Epigastric and intercostal retractions were found on examination of the chest. The chest was dull on percussion. The breath sound was bronchovesicular and soft moist rales was heard in basal region of the both lungs. No wheezing was heard. Cardiac examination revealed no deformity of the precordium. The left cardiac impulse was slightly hyperactive. There was no thrill palpable. The first and second heart sounds were normal. A grade 2/6 pansystolic murmur was heard at the left 3rd and 4th interspace which was radiated along the left sternal border.

Routine blood examination revealed hemoglobin concentration of 11.98 g/dl, WBC

20 400/µl, and platelet count 280,000/µl. The cerebrospinal fluid was colorless, None reaction was positive while Pandy reaction was negative. The CSF cells were absent,. The glucose level was 48 mg/dl while the protein content was 82 mg/dl. Chest x-ray showed no enlargement of the heart but there was evidence of inflammation in both lungs consistent with bronchopneumonia. The electrocardiogram was normal; echo- cardiographic examination have not been done. Skull x-ray also on that time showed the suture was normal and no evidence of craniosynostosis or intracranial calcifi- cations. The working diagnosis was complex febrile convulsion, bronchopneumonia, and multiple congenital defects (microcephaly, VSD, auricle dysgenesis and recto- vaginal fistula).

On February 25, 1997, examination of the sera "TORCH" by complement fixation test was done showing positive IgG anti CMV with total titer of 1:1600. The IgM anti CMV was absent. The IgM or IgG Anti rubella, toxoplasma and HSV2 were negative.

Ultrasound of the head showed enlargement of the lateral and third ventricle. Head CT scan was not done due to financial reason. The patient then was consulted to the Department of Neurosurgery with the conclusion of microcephaly caused by primary brain atrophy and hydrocephalus. The patient was advised for conservative treatment. She was also consulted to the Department of Growth and Development. The DDST showed borderline result. She was treated with ampicillin 250 mg three times daily and phenobarbital 15 mg twice a day for 10 days. ENT examination showed no evi- dence of hearing loss. The final diagnosis was complex febrile convulsion, broncho- pneumonia and multiple congenital defects caused by congenital CMV infection.

Case 2

A 7-month old Balinese boy was admitted to the Child Health Department of Sanglah General Hospital on January 23, 1996 with the main complaint of seizures. The seizures occurred on the average of 5 to 6 times daily, generalized tonic clonic, for 3 to 5 minutes of each seizure. After seizure he was alert. There was no fever. He also vomited after each feeding. The seizure and vomiting started when he was 10 days of age. The patient was able to sit yet and his head was drop in. He was born spon- taneously at term gestational age with body weight of 3200 grams. History of his mother when she was pregnant was not clear because he was adopted.

On the physical examination he was alert with respiration rate, 28/minute, pulse rate, 124 beats/minute and the body temperature was 36.5°C. He was marasmic (50 percentile) with body weight of 4,3 kg. His head was small with head circumference of 33 cm or minus 2 SD bellow the Nellhaus standard. The fontanel has closed already. There was no evidence of strabismus, deviation conjugee or cataract in both eyes. The neck was hypotonic. The chest was symmetrical, the

heart and lungs were normal. The abdomen was flat; the liver and spleen were not palpable. There was evidence of spastic tetraparesis with positive Babinski reflex.

Laboratory examination showed hemoglobin concentration of 13.0 g/dl and WBC 6,000/µl. Serologic examination for TORCH showed positive IgG anti CMV with total titer of 1:400, but the IgM anti CMV and the IgM or IgG anti rubella, toxoplasma and HSV2 were negative. The skull X-ray showed microcephaly where the suture closed. There was no intracranial calcifications.

The working diagnosis was epilepsy, cerebral palsy, marasmus and microcephaly. Then the patient was treated with phenobarbital 10 mg twice daily and multivitamin. Then he was treated with vitamin A 100,000 IU intramuscular and was given gavage feeding of 600 Cal. On consultation to the Department of ENT showed no evidence of hearing loss. EEG examination was consistent with general convulsion.

Head CT scan showed an already closed suture and a hygroma connected with left lateral ventricle leading to the diagnosis of craniosynostosis and porencephaly. The patient was then consulted to the Department of Neurosurgery, confirming the diag- nosis of microcephaly caused by multiple cerebral agenesis. He was advised for con- servative treatment only. The prognosis was considered to be grave. The final diag- nosis was epilepsy, marasmus, microcephaly, cerebral palsy with craniosynostosis and porenchephaly caused by congenital CMV infection.

Discussion

Cytomegalovirus (CMV infection) is the most frequent cause of congenital infection. In humans, occurring in 0.4% to 2.3% of all live birth in the United States, thus con- stitutes a mayor public health problem.[1,3,5] Primary maternal infection often thought not invariable, culminate in transmission to the fetus. The likely sequence of events is maternal viremia resulting in placentitis with subsequent spread to the conceptus. [9]

Gained access to the fetus CMV infection can invade and replicate in virtually every organ, demonstrating a particular affinity for epithelial cell. Occasionally, typical intra- nuclear inclusion are recognized in vascular endothelium. The typical pathologic se- quence is cytolysis with focal necrosis and resultant inflammatory response (mainly mononuclear). Healing may occur with fibrosis reduction number of cell in various organ and occasionally calcification (brain and liver) or with restoration of normal structure in the continued presence of infected. [9,10]

Manifestation in congenital infected infants may range from a severe, rapidly fetal illness to a relatively mild disease with transient symptoms.[9,10] More than 90% of cases of congenital CMV infection detected by virologic screening are asymptomatic in the neonatal period.[11,12] Ten percent of the infected neonates are symptomatic at

birth.[3] The characteristic features are hepatosplenomegaly, hepatitis, jaundice, pete- chie, purpura, thrombocytopenia, pneumonia, small size gestational age, feeding diffi- culties, general failure to thrive, microcephaly, cerebral calcification, chorioretinitis, and sequelae of brain damage. One features alone may be present such as liver dis- ease, thrombocytopenic or brain damage manifestation with or with out motor disabilities.[1,3,8,11,13] The most serious long term sequelae of the neurodevelopmental out come is well documented, includes motor handicap, mental retardation (75%), visual impairment and significant risk for sensory neural hearing loss (33%), which may deteriorate further over time. [3,5,8]

Besides clinical manifestation, the diagnosis of CMV infections may be confirm by one of the following procedure; 1) examination of sediment of fresh urine or gastric contents for presence of the typical inclusion bodies located in the exfoliated cell, 2) biopsy of liver for histologic evidence of typical inclusion bodies, 3) identification of virus in tissue culture, 4) appropriate use of one of the serologic test to the detection of CMV infection anti body such as the neutralizing antibody test, complement fixation (CF), or indirect fluorescent anti body test. [1,14]

There is no effective antiviral therapy currently available for the treatment CMV infections in newborn infants. Clinical trials with several agents have been carried out but the result have been disappointing or difficult to interpret. The most promising antiviral drug is gancyclovir. Passive immunization with, hyperimmune anti-CMV in- fection immunoglobulin and active immunization with alternate CMV infection vaccine represent attractive therapy for prophylaxis against congenital CMV infection.[2]

In our cases the diagnosis of the congenital CMV infection is made based on clinical manifestation and laboratory finding. The clinical manifestation such as complex fibril convulsion, bronchopneumonia and multiple congenital anomalies such as VSD, mi- crocephaly, rectovaginal fistula and auricle dysgenesis in case 1 and epilepsy, ma- rasmus with multiple congenital anomalies such as cerebral palsy, microcephaly with craniosynostosis in case 2. Women who have primary CMV infection during preg- nancy have a 40-50% risk of giving birth to congenital infected infants, 10-15% of these infants will have sequele.[1] Gilles *et al*, have been proved on their study, that there were direct correlation between severity of neonatal infection and presumed duration of the disease in utero. When the infection occurred in second trimester of gestation, the infant born in full term (small for gestation age) or premature, micro- cephaly with or without intracranial calcification, hepatomegaly and disseminated in- travascular coagulation, but when the infection occurred in the third trimester of gestational, the infants were born full-term with out abnormalities. [15]

Besides prenatal CMV infections, the virus also be able to invade the infant peri- natally and postnatally. Perinatal infections are acquired by infant during delivery from exposure to infected maternal genital secretion, postnatally from ingestion of

infected breast milk or iatrogenically as result of blood transfusion.[1] Clinical symptoms of perinatally or postnatally acquired CMV infections including hepatosplenomegaly, limpha-denophaty, or pneumonia. The majority of postnatally infected infants, onset of infection occurred in the first 14 weeks of life.[16] According to that finding, the possibility of perinatally or postnatally acquired CMV infections can be excluded.

In our cases there were no evidence of hepatosplenomegaly, hepatitis, jaundice, petechie, purpura, or thrombocytopenia. That symptoms usually noted in an acute CMV infections.[3,7] The laboratory finding which confirm the diagnosis was evidence of IgG anti CMV infection by Complement fixation test which the total titer, 1:1,600 in the case 1 and 1:400 in the case 2. The IgM anti CMV infections was absent in both cases. Although an IGM antibody response might reasonably be expected in all cases, with the exception of acquisition just prior to delivery, in fact, many neonates with in apparent infections show no macroglobulin antibody. Whether this is a real phenomenon based on reduced viral mass or whether it represents technical difficulties is yet to be answered. Persistence of IgM is variable but likely measured in months.

Whether evidence of increased IgG anti CMV level in both cases was maternally derived or by excessive production as a response of fetal infection in intra uterine, a serial examination of IgG anti body should be done. In the absence of fetal or perinatal infections, maternally derived CF anti body will disappear from the infant's serum at a rate of approximately 1 dilution per month (IgG half life is roughly 30 days). Because maternal antibody titers, in the absence of primary infection, rare exceed 1:128, disappearance of passively transferred antibody should be expected by 6 months in the great majority of uninfected infants.[9] If the amount of IgG anti body does not decline but persist after 6 months of age the presence of the antibody is presumptive evidence of congenital CMV infections.

The diagnosis of congenital infection is best confirmed by isolation of the virus, preferably during the first few days of life. Acquisition of virus at birth may result in shedding as early as 3 weeks and frequently, by 8 week thereby rendering this assay less specific for intrauterine infection with advance age of the patient.[9,17] The preferred site for isolation attempts is urine, although virus is recoverable from throat, conjunctiva, and rectal swabs as well as from white blood cell.9 Because the age of those cases was more than 3 weeks and the limitation of laboratory that available for this purpose, made the isolation of the virus have not been done. Are they still be able to infect the environment, it is according to the finding of the CMV infection in the urine, blood or gastric contains by tissue cultures. CMV infections may persist in urine for prolonged period of time as long as 52 months.[18] Because this examination have not been done, so the ability to infect the environment can not be ascertained.

Also on ENT consultation of both cases there were no evidence of hearing loss, but there was right auricle dysgenesis in case 1. Although it was absent, but such in- fection potentially to cause hearing impairment in a long period after birth. Hicks et al, on their auditory screening of new born found that, 2(14%) of 14 children with sen-

sory-neural hearing loss caused by CMV infection, most of them was not apparent in the new born period.[5,6] Primary report on the out come of infant infected with CMV infection, by 2-4 years old, 5 to 15 percent of these infected infants have developed mental abnormalities including sensorineural hearing loss, microcephaly, motor de- fects such as spastic diplegia or quadriplegia mental retardation, chorioretinitis and dental defect.[1] Other authors reported that the probability of hearing disability was approximately 30% in symptomatic and 13% in the more common asymptomatic infant with congenital infections.[19]

Microcephaly was found in both cases and craniosynostosis in case 2. It was not caused by primary craniosynostosis, but by multiple cerebral agenesis (porencephaly) in case 2 and by primary brain atrophy in case 1. This serious damage of the brain also caused spastic cerebral palsy and epilepsy as in case 1. Prolonged excretion of the virus in congenital CMV infection have been verified and damage may continue after birth. It has been suggested that the most serious damage to the fetus is noted when the maternal infection occur during the first six months of gestation.[13]

Besides central nervous system, CMV infection also affected gastrointestinal system and cardiovascular system. The gastrointestinal system involvement usually are biliary atresia, esophageal atresia, megacolon, omphalocele, cleft palate, stenosis of the ileal and colon and malformed pylory.[1,18] In case 1 involvement of the gastrointestinal system is a recto vaginal fistula.

The cardiovascular defects usually ASD, VSD, tetralogy of Fallot, and PDA. [9,18] In case 1 there was also evidence of VSD. Microcephaly, neurologic defect and congenital heart disease were also found in congenital rubella[1,9,14] but absent of the IgM and IgG anti rubella in both cases, made this agent can be excluded as a cause of infection.

The symptoms of congenital toxoplasmosis also resembles to congenital CMV infection, but toxoplasmosis is likely to be associated with chorioretinitis, microph- thalmia, scattered cerebral calcification and hydrocephalus.[1] Because absent of the IgM and IgG anti toxoplasma in both cases made the possibility of congenital toxoplasmosis can be excluded. So the multiple complications of those cases were caused by congenital CMV infection.

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