International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2020): 7.803

Congenital Citomegalovirus Infection in Eleven Months Old Boy: A Case Report

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Abstract: ***Congenital cytomegalovirus (CMV) infection is the most common cause of neurological handicapped in pediatric. This infection can be symptomatic and asymptomatic. A symptomatic infection will result in worsen prognosis for severe neurological handicapped. Case: We reported an 11-month-old baby with a history of jaundice since birth, abdominal enlargement dan small head circumference. From the physical examination, we found hepatomegaly, lien Schuffner 2, and microcephaly with head circumference below -2 SD since birth. The patient still can respond to auditory and visual stimulus. Laboratories examination reveal reactive anti-CMV IgG and non-reactive anti-CMV IgM. Further examination shows quantitative PCR beyond the normal range for CMV-DNA. Other examination showed leukocytosis, anaemia, thrombocytopenia, prolonged hemostatic function, proteinuria, hemoglobinuria, bilirubinuria, high level of procalcitonin, hypo-albumin, elevated liver function, elevated direct, indirect, and total bilirubin, high level of alkali phosphatase and gamma GT and low level of total protein and globulin. The patient was diagnosed with congenital CMV infection with liver failure, hypo-albumin and prolonged hemostatic function. The patient was planned to treat with intravenous ganciclovir. Patient was died because of acute respiratory distress of pneumonia before treatment. Conclusion: We reported a caseofcongenital CMV infectionwhichemphasize in antiviraltreatmentwithganciclovir. Excellent timing and suitable indication will result in a better prognosis for the neuro developmental outcome and long-term risk of handicapped. Patient was died before treatment.***

Keywords: congenital CMV infection, ganciclovir, valganciclovir

1. Introduction

Cytomegalovirus (CMV) infection is one of the prenatal and perinatal infections that can occur and classified as a TORCH infection (Toxoplasma gondii, Rubella virus, Cytomegalovirus, Herpes simplex virus).[1] TORCH infection is the most common cause of a poor obstetric history in the mother and causing many congenital abnormalities in infants.[2,3] Cytomegalovirus infection is caused by human Cytomegalovirus, which is a DNA virus that is a part of the herpesviridae family. This virus is called cytomegalovirus due to infected cells will double up to the size of uninfected cells. Cytomegalovirus invades host cells and then replicates themself.[2] Congenital CMV infection causes a quite high morbidity in newborns. CMV infection is widespread throughout the world, both developed and developing countries. CMV infection occurs in 0.2-2.4% of all live births in the world and occurs in 0.6-0.7% of all live births in developed countries.[4,5] Cytomegalovirus infection causes developmental disorders of organs in fetus and is the most common cause of hearing loss, neurodevelopmental disorders, and mental retardation in children.[6]

Cytomegalovirus transmission can occur horizontally (from one person to another) or vertically (from mother to fetus). Cytomegalovirus infection is transmitted horizontally through body fluids and requires close contact with body fluids that have been contaminated with CMV. Cytomegalovirus transmission occurs vertically via intrauterine, i.e. through transplacental pathways with CMV viremia in the maternal circulation, intrapartum transmission, i.e. fetal exposure to cervical and vaginal secretions containing CMV during labour and postnatal transmission, i.e. through ingestion of breast milk containing CMV or through blood transfusion contaminated with CMV.[3,7] Vertical CMV infection is the etiology of congenital CMV infection. Congenital CMV infection can be symptomatic and asymptomatic. If the infection is symptomatic, it will lead to worse prognosis and a higher risk for severe neurological disability. Neurological disabilities that can occur include sensorineural deafness, mental retardation, microcephaly, developmental delay, seizure symptoms and cerebral palsy.[3,8,9]

Some findings that can be found in congenital CMV infection include thrombocytopenia,petechiae, hepatomegaly, splenomegaly, intrauterine growth retardation, the presence of hepatitis seen from an increase in liver function and bilirubin, as well as the involvement of the central nervous system (microcephaly, radiographic abnormalities that indicate CMV disease in the central nervous system, CSF abnormalities based on age, chorioretinitis, auditory deficits detected by brainstem-evoked response.[2,7,10]To established a diagnosis other than history and physical examination, must also carry out supporting investigations.Examinations supporting the gold standard for congenital CMV infection is by viral culture in the first three weeks of life from a urine or saliva sample. The examination available in Indonesia today is by qualitative and quantitative polymerase chain reaction (PCR) and serological tests.[10,11]

Provision of therapy is indicated for infants with symptomatic congenital CMV infection, infants with positive CMV PCR tests and infants with impaired organs or central nervous system involvement, including sensorineural deafness. While infants with mild asymptomatic or symptomatic infections without central nervous disorders are not recommended.[7, 8, 12] The recommended therapy is to administer antiviral ganciclovir agents intravenously for six weeks. Ganciclovir therapy for six weeks can prevent hearing loss at the age of 12 months, and improve the development of the baby. Another treatment is valganciclovir, a prodrug of ganciclovir which is rapidly hydrolyzed to ganciclovir after oral administration, showing ten times greater bioavailability than oral ganciclovir.[13-16]

Studies by Kimberlin et al. show that administration of ganciclovir results in a longer duration of hospitalization and shows ten times greater bioavailability than oral ganciclovir.[13-16] Studies by Kimberlin et al. causing haematological side effects such as leukopenia, neutropenia and thrombocytopenia.[13] Studies comparing the effectiveness of ganciclovir and valganciclovir are still very limited, from this evidence-based case report it will be explained whether oral valganciclovir has the same effectiveness as intravenous ganciclovir and the impact of ganciclovir on the improvement of delayed neurodevelopment of cases in infants with congenital CMV infection.

2. Case Report

An 11-month-old baby boy is referred to our hospital with a history of jaundice from birth. The patient has an enlarged abdomen since the age of three months and small head circumference. Previously the patient had received treatment at the other hospital with complaints of jaundice, weak and seizure. At that time, the patient was diagnosed with malnutrition, congenital rubella infection and intrahepatic cholestasis from a two-phase ultrasound result with a suspected cytomegalovirus infection as a cause of cholestasis.

Physical examination showed that patients with vital signs were within normal limits. From the liver and abdominal examination, hepatomegaly was found with the liver enlarging four fingers under the arcus costae and spleen Schuffner 2. The patient had microcephaly with head circumference below -2 SD since birth. Patients can still respond to sound (not deaf); patients can still see the direction of stimulation (not blind). Patient's defecation and urination under normal conditions, normal colour. From a neonatal history, the patient had a birth weight of600gram, length 49 centimetres and head circumference 29 centimetres.

Table 1: Laboratory result on 6 June 2020

Parameter	Value	Unit	Reference range	Note
WBC	14,92	10^3/µL	4,1-11	High
Neutrofil%	57,05	%	18,30-47,10	High
Limfosit%	36,06	%	30,00-64,30	Normal
Monosit%	5,96	%	0,0-7,10	Normal
Eosinofil%	0,11	%	0,0-5,0	Normal
Basofil%	0,81	%	0,0-0,70	High
Neutrofil#	8,51	10^3/µL	1,10-6,60	High
Limfosit#	5,38	10^3/µL	1,80-9,00	Normal
Monosit#	0,89	10^3/µL	0,00-1,00	Normal
Eosinofil#	0,02	10^3/µL	0,00-0,70	Normal
Basofil#	0,12	10^3/µL	0,0-0,10	High
RBC	3,15	10^6/µL	3,90	Low
HGB	9,70	g/dL	12-16	Low
HCT	28,07	%	36-46	Low
MCV	89,13	fL	80-100	Normal
MCH	30,79	pg	26-34	Normal
MCHC	35,54	g/dL	31-36	Normal
PLT	98,78	10^3/µL	140-440	Low
Procalcitonin	0,32	ng/mL	<0,15	High
Albumin	2,30	g/dL	3,50-5,20	Low

Several laboratory examinations were carried out in the patient, such as anti-CMV antibodies, which resulted in IgG anti-CMV reactive and non-reactive IgV anti CMV. Further examination was carried out, confirmation with blood PCR obtained 4.84 x 10^3 where under normal conditions it should not be detected. Complete blood test results showed the presence of leukocytosis, anemia and thrombocytopenia (Table 1). From a urine analysis, proteinuria, hemoglobinuria, and bilirubin were present in the urine (Table 2). From the results of other investigations, it was found increased procalcitonin, hypoalbumin, prolonged haemostasis function, increased liver function, direct bilirubin, indirect and total increased, increased alkaline phosphatase and gamma GT and low level of total protein, albumin and globulin. (Table 3).

Patients were diagnosed with congenital CMV infection with liver failure and increased liver function, a history of hypoalbumin, and prolonged hemostasis function. The patient is planned for the administration of intravenous ganciclovir therapy.

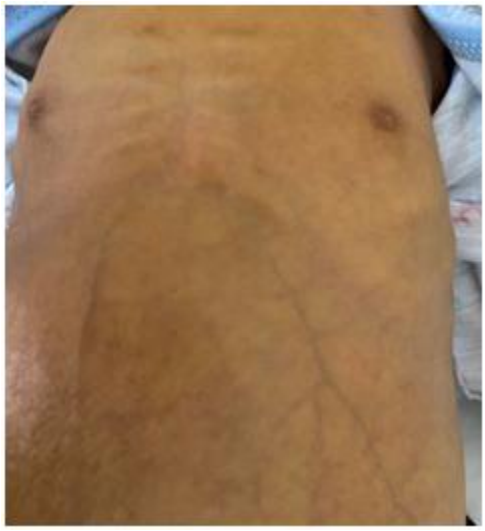


Figure 1: The patient clinical picture with hepatomegaly and ptechie

Figure 2: The patient clinical picture with microcephaly and hepatomegaly

Table 2: Urine analysis result (9 June 2020)

Parameter	Value	Unit	Reference range
Density	1,016		1,003-1,035
Cloudy	cloudy (+)		
pH	6,50		4,5-8
Leukocytes	Negative	Leuco/µL	Negative
Nitrite	Negative	mg/dL	Negative
Protein	(+1)	mg/dL	Negative
Glucose	Negative	mg/dL	Negative
Ketone	Negative	mg/dL	Negative
Blood	(1+)	mg/dL	Negative
Urobilinogen	Normal	mg/dL	Negative
Bilirubin	(3+)	mg/dL	Negative
Crystal	Negative	/LPB	
	Another Bacteria ++	/LPB	
Warna	Dark yellow		Yellow

Table 3: Laboratory result (17 June 2020)

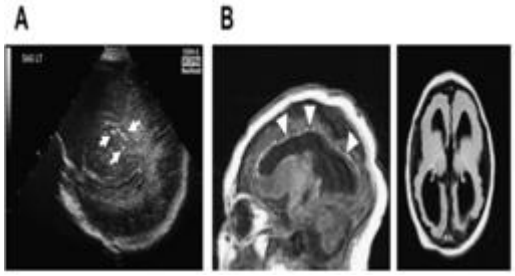
Parameter	Value	Unit	Reference range	Note
PPT	42,1	Detik	4,1-11	High
INR	3,11		0,9-1,1	Very high
APTT	78,9	Detik	24-36	High
AST/SGOT	347,5	U/L	11-33	High
ALT/SGPT	91,10	U/L	11-50	High
Total bilirubin	26,88	mg/dL	0,00-1,00	High
Direct bilirubin	15,50	mg/dL	0,00-0,30	High
Indirect bilirubin	11,38	mg/dL		High
Alkali phospatase	617	U/L	0-462	High
Total protein	4,3	g/dL	5,10-7,30	Low
Albumin	2,90	g/dL	3,50-5,20	Low
Globulin	1,40	10^6/µL	3,2-3,7	Low
Gamma GT	51	g/dL	12-16	High

3. Discussion

Congenital cytomegalovirus (CMV) infection is an infection caused by human Cytomegalovirus, which is a DNA virus that belongs to the herpesviridae family. CMV infections are widespread throughout the world, both developed and developing countries.[1-3] Cytomegalovirus infections occur in 0.2-2.4% of all live births in the world and occur in 0.6-0.7% of all births live in developed countries.[4-5]Cytomegalovirus infection can be symptomatic and also asymptomatic. Most children born with congenital CMV infection are asymptomatic at birth. Asymptomatic, in this case, is defined as the detection of CMV in any body fluids in children in the first three weeks of life but does not show abnormalities in the clinical, laboratory, and radiological examination results. Children who show symptoms of congenital CMV infection at birth only range from 7-10%.[1-3] Risk factors associated with an increased risk of congenital CMV infection are maternal age that is too young during pregnancy, low patient socioeconomic status, and occupation as caregivers in daycare.[4] In this case, risk factors for infection have not yet been identified.

Infants with congenital CMV infection most often show three clinical manifestations, the presence of jaundice (62%), petechiae (58%), and hepatosplenomegaly (50%) which is called triad congenital CMV infection.[7,10] In this case, the patient, was complained of jaundice since at birth and having an enlarged abdomen, where physical examination found hepatomegaly with an enlarged liver of 4 fingers under the arcus costae. Other clinical symptoms found in congenital CMV infection are fetal hydrops, premature birth, stunted fetal growth, clinical manifestations of the skin in the form of purpura and petechiae called blueberry muffin spots, the presence of microcephaly, lethargy, spasms, hypotony and hearing loss in the form sensorineural deafness.[2,7,10] In this case, another symptom found in the patient is microcephaly with the patient's head circumference below -2 SD. Clinical manifestations of the skin were not found in these patients. The patient in this case report was also born aterm with a birth weight of 2,600 grams. Chorioretinitis and hearing loss are not found in patients. Patients can still respond to sound (not deaf); patients can still see the direction of stimulation (not blind).

The gold standard examination for the diagnosis of congenital CMV infection is isolation or viral culture in children within the first three weeks. Samples were taken for virus isolation from urine, saliva, cervicovaginal secretions, amniotic fluid, blood, and cerebrospinal fluid. Other investigations that can be done is polymerase chain reaction (PCR) examination of urine or salivary samples with a sensitivity of 89% and specificity 96%.[1,2,7,11] In this case, the patient has a quantitative PCR examination result 4.84 x 10^3, which under normal conditions should not be detected.



Picture 2: Neuroimaging examination in patients with congenital CMV infection. (A) is the head ultrasound where intracranial calcification of the periventricular is indicated by arrows. (B) Head MRI results in infants with congenital CMV infection, sagittal (left) and axial (right) cuts indicate ventriculomegaly, periventricular calcification and reduced brain volume (reduced white matter).[7]

Laboratory tests for congenital CMV infection will show anemia, thrombocytopenia, elevated liver enzymes, hyperbilirubinemia and from lumbar puncture examination will show an increase in protein in the cerebrospinal fluid.[2,7,10] I
n this case, complete blood tests show leukocytosis, anemiaand thrombocytopenia. Examination of liver function and bilirubin showed an increase in SGOT, SGPT, direct, indirect and total bilirubin increased. Other abnormal laboratory results found in patients have increased procalcitonin, prolonged haemostasis, increased of alkali phosphatase, gamma GT, hpoalbumin and low total protein and globulin. Lumbar puncture examination to assess cerebrospinal fluid is not done in patients.

From the radiological examination, plain chest radiographs sometimes revealed pneumonia and neuroimaging examinations such as CT scan, head MRI and ultrasound show intracranial calcification in the periventricular, thalamus and cortical sections as shown in Figure2.[8,10] Also

found in ventriculomegaly and cortical dysplasia. In this case, radiological and neuroimaging examinations such as CT head scans have not been performed.

Some literature shows that immunoserological examination of anti-CMV IgG and IgM can support the diagnosis of congenital CMV infection if there is positive anti-CMV IgM or an increase in anti-CMV IgG levels up to 4 times the normal value. However, anti-CMV IgG and IgM immunoserological examinations are not recommended for diagnosis of congenital CMV infection. That is because anti-CMV IgG detected in children is most likely maternal anti-CMV IgG antibodies that cross the placenta and can last up to 18 months of age, whereas anti-CMV IgM often shows false-positive results against other viral infections, especially EBV infections (Epstein-Barr virus) and HHV-6 (Human Herpes virus 6). [2,7,10] In this case, serological examination showed the results of reactive IgG CMV anti-CMV and non-reactive IgM anti-CMV.

Management of children with congenital CMV infection includes supportive management. Breastfeeding should be sought for children. Transfusion of red blood cells or platelets can be given if there is severe anemia or severe thrombocytopenia. Children can be treated in intensive care if needed.[2,7,8,10] Antivirus given to treat CMV infection that is known at present is ganciclovir intravenously at a dose of 6 mg/kgBW/day every 12 hours or oral valganciclovir at a dose of 16 mg/kgBW/day every 12 hours.[7,13-19] Some literature states that the antiviral is given for six weeks, but the administration of antiviral for six weeks is not always recommended. Provision of antiviral for two weeks has had a good impact on the course of childhood diseases, and additional doses for the next 1-2 weeks can be given if the symptoms and signs in children do not decrease. Periodic evaluations should be carried out on children to determine the development of CMV infectious disease. The evaluation included a neuroimaging examination as well as hearing and vision functions.[15,16,19] In this case, the patient was planned for intravenous administration of ganciclovir. But the patient died before therapy was given.

The prodrug form of ganciclovir is valganciclovir administered orally. Studies have shown that valganciclovir shows ten times greater bioavailability than oral ganciclovir.[15, 16.] Study by Kimberlin et al. showed that administration of ganciclovir results in a longer duration of hospitalization and causes haematological side effects such as leukopenia, neutropenia and thrombocytopenia.[13] To see whether the effectiveness of oral valganciclovir is as good as oral ganciclovir, we conducted a scientific study and obtained an evidence-based study entitled ***"Efficacy of Valganciclovir versus Ganciclovir in treatment of symptomatic cytomegalovirus infection in infants: An open-label randomized controlled trial"*** by Fatema K et al. on JICNA 2019. This journal is valid, important and can be applied (level of evidence 1B with recommendation A). This paper concludes that both valganciclovir and ganciclovir have almost the same efficacy in the management of symptomatic congenital CMV infections. These drugs show the same high efficacy for visual and hearing function outcomes. However, valganciclovir has a better effect on improving cognitive function and has more minimal side effects compared to ganciclovir.[13]

Symptomatic congenital CMV infection has a worse prognosis, namely the presence of a neurological disability and developmental delay.[9,10] The administration of ganciclovir therapy is known to provide improvement in disability or sequelae in patients to explain the impact of ganciclovir therapy on the improvement of neurological developmental disorders in infants with our congenital CMV infection. We did a research study and obtained an evidence-based study with title ***"Neurodevelopmental Outcomes Following Ganciclovir Therapy inSymptomatic Congenital Cytomegalovirus Infections Involving the Central Nervous System"*** by Oliver SE et al. in the Clinical Virology Journal in 2009. This journal is valid, important and can be applied (evidence level 1B with recommendation A). The journal concluded that infants with congenital CMV infection with central nervous system involvement receiving intravenous ganciclovir therapy had developmental delays at ages 6 and 12 months lower than infants who did not receive therapy. Intravenous ganciclovir for six weeks can be recommended for the management of infants with symptomatic congenital CMV infection with central nervous system involvement. Treatment should begin in the first month of life, and patients must be closely monitored for toxicity such as neutropenia.Because previous data only show management for infants with congenital CMV infection with central nervous system involvement, this data cannot be used for other manifestations of CMV infection such as asymptomatic infants or without central nervous system involvement.[9] In this case, patients with microcephaly indicate that there is the involvement of infection with the central nervous system so intravenous ganciclovir is recommended. But the patient died before therapy was given.

4. Conclusion

We reported an 11-month-old baby with a history of jaundice since birth, an enlarged abdomen since three months and a small head circumference. Physical examination showed hepatomegaly and Schuffner's spleen 2. Patients had microcephaly with head circumference below -2 SD since birth. Patients can still respond to sound (not deaf); patients can still see the direction of stimulation (not blind). The results of laboratory tests showed the presence of anti-reactive IgG anti-CMV and non-reactive IgM anti-CMV. Further examination was carried out a confirmation with blood PCR obtained more than the normal limit. Other examination results showed leukocytosis, anemia and thrombocytopenia, proteinuria, hemoglobinuria bilirubinuria, increased procalcitonin, hypoalbumin, lengthened haemostasis, increased liver function, increased direct bilirubin, indirect and total hemoglobinuria and increased gamma GT and total protein, albumin and globulin in the globally low grade. Patients diagnosed with congenital CMV with liver failure and increased liver function, a history of hypoalbumin, and prolonged haemostasis and planned administration of ganciclovir therapy.

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