Original Article

Ganciclovir Treatment in Symptomatic Congenital CMV Infection at Siriraj Hospital: 11 Year-Review (2008 to 2019)

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Background: Congenital cytomegalovirus (CMV) infection is the most common non-genetic cause of permanent sensorineural hearing loss in infants and children. A 6-month course of intravenous ganciclovir or valganciclovir is recommended for treatment of patients with moderate to severe symptomatic congenital CMV disease. Hearing status improvement has been reported in those that received treatment within the first month of life. In Thailand, there has been no data of antiviral treatment in symptomatic congenital CMV patients.

Objective: To determine the incidence of symptomatic congenital CMV infection in the past 11 years and to evaluate the hearing, neurological, and developmental outcomes of the antiviral treatment and factors associated with hearing outcomes.

Materials and Methods: A retrospective observational study was performed at Siriraj Hospital, between January 2008 and December 2019. The medical records of the patients diagnosed of symptomatic congenital CMV infection (ICD10-P351) were reviewed.

Results: The incidence of symptomatic congenital CMV infection was 0 to 1.01 case per 1,000 livebirths. Of the 52 patients, 18 received 6-week course of ganciclovir and five continued with oral valganciclovir for three to six months. Developmental delayed was found in 69.2% (36). No difference in hearing outcomes at 6 and 12 months of age between the patients who did or did not receive treatment. Among 24 (46.1%) children who underwent hearing test at two to three years of age, the birth characteristics, as well as antiviral treatment (attributable risk 0.007, 95% CI –0.4 to 0.4, p=0.973), had no difference in hearing outcome. Long-term disability was diagnosed in the lower proportion among the patients receiving antiviral treatment (attributable risk –0.3, 95% CI –0.5 to –0.1, p=0.030).

Conclusion: Symptomatic congenital CMV infection resulted in poor hearing and developmental outcomes. Antiviral treatment reduced risk of disability but did not improve hearing outcomes. The results underscore the need for early diagnosis and initiation of antiviral treatment in infants with symptomatic congenital CMV.

Keywords: Congenital infection; CMV; Hearing loss; Ganciclovir; Valganciclovir; Disability

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Cytomegalovirus (CMV) is the most common cause of congenital infection in developed countries[1]. Incidence of congenital CMV infection in the United State is 40,000 birth cases per year[1,2]; however, the data in developing countries including Thailand have been limited.

The clinical symptoms at birth of congenital CMV infection appeared in about only 10% of all cases[2], including hepatosplenomegaly, microcephaly, intracerebral calcification, sensorineural hearing loss (SNHL), retinitis, and developmental delayed in later infancy and early childhood[3]. Congenital CMV may cause significant disabilities. SNHL is the most common sequelae occurring up to 50% of symptomatic congenital CMV infection. For those 90% who are asymptomatic patients, they may still develop SNHL in up to 15%[2]. Congenital CMV infection is the most common cause of permanent deafness in infant and children. This leads to substantial developmental problems and global burden of disease[4]. CMV is responsible for 25% of all non-genetic causes of deteriorated SNHL in the first four years of life[4].

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Antiviral treatment with intravenous ganciclovir and valganciclovir with oral prodrug of ganciclovir, have been approved for treatment of symptomatic congenital CMV infection[5]. A randomized controlled study in the United States revealed a 6-weeks ganciclovir treatment in symptomatic patients involving central nervous system (CNS) improved audiologic outcomes at six months[6]. A randomized placebo-controlled trial study comparing 6-week and 6-month course of valganciclovir found that longer duration resulted in hearing improvement at 6- and 12-month of ages and better neurodevelopmental score at 24-month of ages[7]. A 6-month course of ganciclovir or oral valganciclovir has been recommended for treatment of patients with moderate to severe symptomatic congenital CMV disease and should be started within the first month of life[5]. Therapy is not recommended in the asymptomatic patients. Lack of data suggests benefit in mild symptomatic disease or in isolated SNHL[5]. The most common side effect of ganciclovir and valganciclovir is bone marrow suppression, and some patients need to withhold the treatment[5]. Despite of recent recommendation of 6-month course of valganciclovir, most resource-limited settings have been unable to afford the treatment.

In the present study, the authors aimed to determine the incidence of neurologic and hearing outcomes of symptomatic congenial CMV infection in a tertiary hospital in Thailand. The authors also evaluated the utilization and effects of ganciclovir and valganciclovir treatment in Thailand setting.

Material and method

A retrospective medical chart review was conducted in patients with the diagnosis of symptomatic congenital CMV infection (ICD10-P351) between January 2008 and December 2019 at the Department of Pediatrics, Faculty of Medicine, Siriraj Hospital, a tertiary care center in Bangkok, Thailand. The present study was approved by the Institution Review Board (certificate of approval number Si 302/2019).

The clinical data obtained from the medical record included evidence leading to diagnosis of congenital CMV infection, with microbiologic confirmation defined as positive urine CMV isolation test within 3-week of life, or without microbiologic confirmation defined as presence of clinical and radiologic features compatible with congenital CMV infection plus positive CMV serology in patients older than three weeks of age[8]. The clinical presentation, antiviral treatment, hearing test results, and neurological and developmental progression were collected. The authors also contacted the parents of those who did not return for follow-up at the study center for any hearing test results performed at other medical center and developmental progression.

The hearing outcome was routinely evaluated at newborn period and follow-up at 6- and 12-months, and at two to three years of age as per recommendation[9]. The hearing outcomes were classified into normal and hearing loss using the updated American Speech-Language-Hearing Association Criteria[10]. The results were categorized into normal or abnormal hearing if evaluated only once, and improvement of at least one side of the ears, or hearing deterioration if evaluated more than once. Disabilities was a diagnosis by pediatricians or pediatric neurologists defined as impairment in physical, mental, vision, hearing, cognition, communication, developmental, or other conditions that interfere with patient's ability to engage in certain actions, and requires special helps in some other ways of patient's daily life[11,12]. Global delay development was defined as delay in at least two aspects of development[13].

Descriptive statistical analyses were performed using Stata, version 11.2 (StataCorp LP, College Station, TX, USA). The incidence of symptomatic congenital CMV infection was determined by the number of cases born at Siriraj Hospital with the denominator of number of livebirths at Siriraj Hospital. Univariate and multivariate analyses were used to explore factors potentially associated with hearing outcomes. The Mann-Whitney U test was used to compare continuous variables, while Pearson's chi-square or Fisher's exact test was used to analyze dichotomous variables. Kaplan Meier estimation was used to analyze the proportion of improvement of hearing outcomes.

Results

Fifty-two cases were included in the present study, of which 35 (67.3%) had microbiologic confirmation and 47 cases were born at Siriraj Hospital. The overall incidence of symptomatic congenital CMV in the11-year period was 0.4 cases per 1,000 births, varying between 0 and 1.01 case per 1,000 livebirths each year.

There were 19 (36.5%) patients born prematurely, before 37 weeks of gestation, 38 (73.1%) patients were born with low birth weight below 2,500 grams, and 40 (76.9%) patients were small for gestational age. Clinical presentations at birth are summarized in Table 1. Small for gestational age (90.3%)

Table 1. Clinical manifestations of symptomatic congenital cytomegalovirus infection

Signs and symptoms	Total (n=52); n (%)
Small for gestational age	47 (90.3)
Microcephaly	38 (73.0)
Hepatobiliary*	38 (73.0)
Hematology**	26 (49.2)
Rash***	20 (38.4)
Congenital heart problems****	21 (40.3)
Hypoglycemia	14 (26.9)
Respiratory distress	14 (26.9)
Neonatal sepsis	6 (11.5)
Neurology*****	5 (9.64)
Necrotizing enterocolitis	3 (5.8)

* Hepatomegaly 15 cases, splenomegaly 11 cases, hepatitis 6 cases, cholestasis jaundice 6 cases; ** Anemia 15 cases, thrombocytopenia 11 cases; *** Generalized petechiae 10 cases, nonspecific rash 4 cases, generalised ecchymosis 3 cases, blueberry muffin rash 3 cases; **** PDA 14 cases, ASD 5 cases, VSD 2 cases; ***** hypertonia 3 cases, seizure 2 cases

and microcephaly (73%) were the most common presentations. Eighteen patients received 6-week course of intravenous ganciclovir treatment. Of these, five patients extended their treatment with oral valganciclovir to four or five months in four patients and to six months in one patient.

Of the 24 (46.1%) patients who had hearing tests performed, 11 (45.8%) had abnormal hearing or hearing deterioration. There was no difference in the birth characteristics between the two groups of

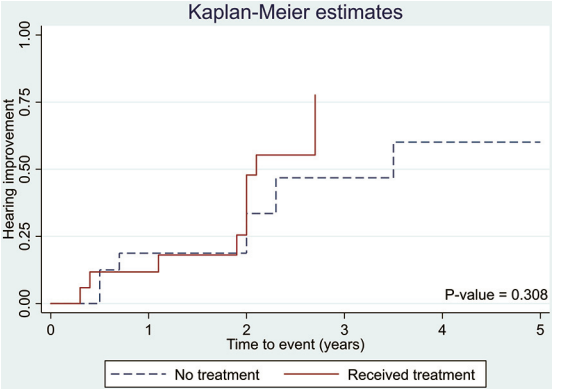

Figure 1. The proportion of improvement of hearing outcomes.

The hazard ratio (95% CI) of 1.7 (0.6 to 4.9), p=0.308

hearing outcomes (Table 2). There was no difference in the hearing outcomes at 6-, 12-, and 24-month age between antiviral treated and untreated group [hazard ratio (95% CI) of 1.7 (0.6 to 4.9), p=0.308] (Figure 1).

Three cases required hearing aids, one at 2 years 8 months of age in the antiviral treated group with profound hearing loss both ears, one at 11 years of age in the untreated group with severe hearing loss both ears, and one at 2 years 6 months of age in the untreated group with profound hearing loss both ears.

The patients with more clinical symptoms were more likely to receive antiviral treatment. Developmental delayed or abnormalities were found in 36 (69.2%) patients, and most were affected by abnormal speech. Microcephaly was found in 38 (73%) and epilepsy in 12 (25%) patients. Three patients

Table 2. Factor associated with hearing outcomes at 2 to 3 years of ages

Factors	Total (n=24); n (%)	Normal or best ear improvement (n=13); n (%)	Abnormal or deteriorated (n=11); n (%)	Relative risk (95% CI)	Attributable risk (95% CI)	p-value
Newborn status						
Term	18 (100)	10 (55.6)	8 (44.4)	1.1 (0.4 to 2.7)	0.05 (–0.4 to 0.5)	0.813
Preterm	6 (100)	3 (50.0)	3 (50.0)	1		
Birth weight						
Normal	6 (100)	4 (66.7)	2 (33.3)	1		
Low birth weight (<2,500 g)	18 (100)	9 (50.0)	9 (50.0)	0.7 (0.4 to 1.5)	–0.17 (–0.6 to 0.3)	0.478
Birth size						
SGA	19 (100)	9 (47.4)	10 (52.6)	1		
AGA	5 (100)	4 (80.0)	1 (20.0)	1.7 (0.9 to 3.2)	0.33 (–0.09 to 0.74)	0.193
Treatment*						
Received GCV/VGCV	11 (100)	6 (54.6)	5 (45.4)	1.01 (0.5 to 2.1)	0.007 (–0.4 to 0.4)	0.973
No antiviral treatment	13 (100)	7 (53.8)	6 (46.2)	1		

SGA=small for gestational age; AGA=appropriate for gestational age; GCV=ganciclovir; VGCV=valganciclovir; CI=confidence interval

* defined as receiving GCV with or without VGCV

Table 3. Analysis of treatment associated to long-term disabilities

Factors	Total (n=52); n (%)	Disabilities (n=19); n (%)	Normal (n=33); n (%)	Relative risk (95% CI)	Attributable risk (95% CI)	p-value
Treatment*						
Received GCV/VGCV	18 (100)	3 (16.7)	15 (83.3)	0.35 (0.12 to 1.06)	–0.3 (–0.5 to –0.1)	0.030**
No antiviral treatment	34 (100)	16 (47.1)	18 (52.9)	1		

GCV=ganciclovir; VGCV=valganciclovir; CI=confidence interval

* defined as receiving GCV with or without VGCV

Table 4. Side effect among participant who received treatment

	Total (n=18); n (%)	Ganciclovir 6 weeks (n=13); n (%)	Ganciclovir 6 weeks and valganciclovir up to 3-6 months (n=5); n (%)
Experience at least one side effect	15/18 (83.3)	10/13 (76.9)	5/5 (100)
Anemia	14/18 (77.8)	9/13 (69.2)	5/5 (100)
Neutropenia	7/18 (38.9)	5/13 (38.5)	2/5 (40.0)
Thrombocytopenia	8/18 (44.4)	6/13 (46.2)	2/5 (40.0)
Transaminitis	6/18 (33.3)	5/13 (38.5)	1/5 (20.0)

were diagnosed of cognitive impairment and mental retardation and two patients with attention deficit and hyperactivity disorder. Of the 31 patients with imaging scan available, periventricular calcification was found in 23 (74.2%), ventriculomegaly in three (29%), and cystic lesion in 15 (16.1%) patients.

At the median age of 3.5 years with a range of 1 to 10 years, 19 (36.5%) patients had disability. The patients who received antiviral treatment had less proportion of disability than those who did not receive treatment [16.7% versus 47.1%, relative risk ratio of 0.35 (0.12 to 1.06), attributable risk –0.3 (–0.5 to –0.1), p=0.030] (Table 3). Side effects of ganciclovir and valganciclovir are shown in Table 4. Anemia was found in 14 out of 18 (77.7%) treated patients, including all cases who received valganciclovir, and one of them required blood transfusion. Neutropenia occurred in seven cases (38.8%) and three of them had to discontinue the treatment for approximately 7 to 12 days before re-initiated. Thrombocytopenia without clinical bleeding occurred in eight cases (44.4%). Transient transaminitis occurred in six patients (33.3%).

Discussion

The incidence of symptomatic congenital CMV infection in the present study setting was low but associated with devastating neurologic and developmental abnormalities that resulted in long-term disabilities. A meta-analysis from 37 study groups reported overall, the combined birth prevalence of congenital CMV was 0.64%, but varied from 0.0 to 25.8%, among different study populations[15]. The authors found about half of the patients had abnormal hearing, two-third had developmental abnormality particularly in speech, and a third had long-term disability. This proportion is higher than previously reported in Thailand[16], likely due in part to the present study included only symptomatic infection. There was limited data of hearing and developmental outcome of symptomatic congenital CMV infection in Asian countries. A retrospective cohort study from the Netherlands reported moderate to severe long-term impairment of 53.8% in symptomatic congenital CMV infection[17]. Symptomatic patients were more frequent to have delayed development outcomes especially speech domain and cognitive impairment similar as the authors have found[17]. The microbiologic confirmation of congenital CMV required the testing before three weeks of age and may not be available as the infants appeared normal during neonatal period or born in the hospital without testing capacity. Only 67.3% in the present study cohort had microbiologic confirmation. Imaging scan has been helpful in supporting the diagnosis particularly in the patients who had subtle symptoms at birth and presented beyond the golden period for diagnosis with neurodevelopmental disabilities. The incidence rate in the present report is only the tip of the iceberg representing around 10% of total congenital CMV infection.

Antiviral treatment with ganciclovir or

valganciclovir has been recommended to be initiated within one month of age to improve hearing outcome[5]. All the infants diagnosed before one month of age, after the recommendation was published, received intravenous ganciclovir for six weeks as it is reimbursable under the universal coverage. Due to limited affordability, only five patients received extended treatment of oral valganciclovir following 6-week course of intravenous ganciclovir. Moreover, the preparation process of small doses of valganciclovir to use in young children is at risk of potential teratogen and carcinogen when the tablet was crushed or broken[14]. The treatment was only prescribed in the large hospitals that have safety cabinet for the preparation.

The experience of antiviral treatment in the authors' setting has been limited. From the 18 cases, in comparison to those who were born before the recommendation and did not receive antiviral treatment, there was no benefit on the hearing outcomes from antiviral treatment. However, the antiviral treatment was found to reduce disabilities. This could be from the short duration of treatment with only a small number of patients that received treatment beyond the six weeks. The 6-week treatment was found to be inferior to the 6-month course[7]. Most of the treated patients were temporally paused due to bone marrow suppression, nonetheless, all cases were able to complete the 6-week course of treatment. These side effects were comparable to other reports and could be serious and prone to complications such as severe infection from neutropenia or bleeding from thrombocytopenia.

The present study has several limitations. The interpretation of hearing outcomes has limited power due to missing data due to loss to follow-up. Only 24 (46.1%) had hearing test results available at two to three years of age. The number of patients who received extended ganciclovir and valganciclovir treatment was too small to determine the difference of benefit compared with shorter course of 6 weeks. This may underestimate the benefit of antiviral treatment. Despite the shorter course of treatment received in most of the patients, the authors found that risk of disabilities was reduced by the treatment. Another limitation was that the authors may have missed other factors causing disability from medical record review.

As congenital CMV infection may result in major disability affecting the patients and their family's quality of life, early diagnosis and initiation of effective treatment is compelling. It is important to follow-up the outcomes in these patients as the treatment will be more accessible in the future. Further research on effective prevention and management is underscored.

Conclusion

Symptomatic congenital CMV infection in the present study setting was 0 to 1.01 case per 1,000 livebirths. About half of the patients had hearing deficit and a third had long-term disability. Antiviral treatment reduced the risk of disability but frequently associated with adverse effects, mostly on bone marrow suppression. Measures to improve early diagnosis and early initiation of antiviral treatment should be implemented to improve the outcomes of these children.

What is already known on this topic?

Incidence of congenital CMV infection in the United State is 5 to 10 per 1,000 livebirths per year or approximately 40,000 cases per year. A 6-month course of ganciclovirvalganciclovir has been recommended for treatment of moderate to severe symptomatic congenital CMV disease within first month of life.

What this study adds?

The overall incidence of congenital CMV infection in 11-year at Siriraj Hospital was 0.4 case per 1,000 livebirths each year. Treatment with ganciclovir or valganciclovir, for six weeks or extended for three to six months reduced the risk of long-term disabilities.

Conflict of interest

The authors declare no conflict of interest.

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