http:// ijp.mums.ac.ir
Original Article (Pages: 9085-9094)

Evaluation of the Prevalence of Congenital Cytomegalovirus Infection and its Clinical Outcomes in Neonates Born in Vali-e-Asr Hospital of Birjand, Iran

Tayyebeh Chahkandi [1], *Elaheh Abbasi Yazdi [2], Mohammad Hasan Namaei [3], Bita Bijari [4]

[1]Department of Pediatrics, Faculty of Medicine, Birjand Atherosclerosis and Coronary Artery Research Center, Birjand University of Medical Sciences (BUMS), Birjand, South Khorasan Province, Iran. [2]Resident of Pediatrics, Department of Pediatrics, Faculty of Medicine. Birjand University of Medical Sciences (BUMS), Birjand, South Khorasan Province, Iran. [3]Department of Microbiology, Faculty of Medicine, Infectious Diseases Research Center, Birjand University of Medical Sciences (BUMS), Birjand, South Khorasan Province, Iran. [4]Department of Community Medicine, Faculty of Medicine, Cardiovascular Diseases Research Center, Birjand University of Medical Sciences (BUMS), Birjand, South Khorasan Province, Iran.

Abstract

Background

Cytomegalovirus (CMV) has been known as the most common cause for congenital infections worldwide which can lead to death in fetus and neonates as well as neuropsychiatric deficits. The aim of this study was to determine the prevalence of congenital CMV infection in newly born neonates and to evaluate the medical outcomes.

Materials and Methods

In this cross-sectional study, 868 neonates were selected using unconditional random sampling in 2017. Neonatal saliva was given on the first or second day of birth using a Dacron swab and tested by PCR for the presence of CMV DNA. All infants with positive CMV infection went through further tests and examinations to evaluate the clinical outcomes.

Results: 787 (90.67%) and 81 (9.33%) births were term and preterm respectively. The PCR test was positive results only in 14 term neonates (1.61%). Thus, the prevalence of CMV infection in term neonates (n=14, 1.61%) was higher than that of preterm infants (n=0), although there was no statistically significant difference (P>0.05). The most common abnormalities were neutropenia (50%, n=4) followed by anemia (37.5%, n=3).

Conclusion

The prevalence of CMV infection in this study (1.61%) was within the global range and there was no association between CMV infection and birth weight, infant gender, and as well ae neonatal type. The frequency of symptomatic neonates at birth in this study was higher than the average global range, but almost the same as in developing countries.

Key Words: Congenital Infection, Cytomegalovirus, Prevalence, Neonates.

*Please cite this article as: Chahkandi T, Abbasi Yazdi E, Namaei MH, Bijari B. Evaluation of the Prevalence of Congenital Cytomegalovirus Infection and its Clinical Outcomes in Neonates Born in Vali-e-Asr Hospital of Birjand, Iran. Int J Pediatr 2019; 7(3): 9085-94. DOI: **10.22038/ijp.2018.35425.3103**

Corresponding Author:

Elaheh Abbasi Yazdi (M.D), Student Research Committee, Department of Pediatrics, Faculty of Medicine, Birjand University of Medical Sciences (BUMS), South Khorassan, Birjand, Iran. Postal code:971796151

Email: elaa1363@gmail.com

Received date: Sep.25, 2018; Accepted date: Oct 22, 2018

1- INTRODUCTION

Human cytomegalovirus (CMV) which belongs to the Herpesviridae family, is one of the most common human influenza viruses with a prevalence of 0.64% in births, varying according to one's geographical area, race and socio-economic status (1, 2). Congenital CMV infection occurs by the virus passing through the mother via the placenta and infecting the fetus which has an immature immune system. This infection can cause fetal and neonatal death, cognitive and behavioral disorders, cerebral palsy, and visual and sensory acuity (3, 4). These complications usually mostly occur in the first trimester of pregnancy (1, 5). The virus is highly compatible with human host and has been known as the most common cause of congenital infections worldwide (3, 6). Unfortunately, most of these diseases occur in adults with minimal signs and symptoms and their identification can only be done by performing serological tests (7). After entering the human body and causing an initial infection, CMV remains in blood's monocyte cells and can be transmitted to others. After an initial infection, an Immunoglobulin G (IgG) antibody is produced and remains positive until the end of one's life (8, 9).

The virus can be transmitted through body fluids such as saliva, urine, blood, semen, and cervical secretions. This transmission in neonates may occur during delivery by passage through the delivery channel or post-delivery via contact with contaminated discharge or contaminated milk intake (10). The prevalence and incidence of CMV infection has shown to be higher among ethnic minorities and lower socioeconomic class (3, 11). The prevalence in Asian-African women is up to 80% and in European-American women is up to 65% (12). The classic clinical symptoms of congenital CMV infection include intrauterine growth retardation, microcephaly, hepatosplenomegaly, peptic ulcer, jaundice, corytrenitis, thrombocytopenia, anemia, and other atypical symptoms (1). Laboratory findings have shown increased transaminases, thrombocytopenia, congenital hyperbilirubinemia, elevation of the cord blood Immunoglobulin M (IgM), atipic lymphocytes and elevated protein levels in the spinal fluid (13). Definite diagnosis of CMV infection is confirmed by separating the virus from urine or saliva in the first and second week of birth (14).

Considering the prevalence of CMV infection and its irreversible and costly complications and consequences, it is necessary to obtain further information about other possible symptoms of the disease, various diagnostic methods, its transmission routes, and mixed symptoms accompanying the disease that could confirm other diagnosis as well. Moreover, there has not been any concise statistics regarding the prevalence of this disease in Iran, specifically in Birjand (Capital city of South Khorasan located in East of Iran). Thus, the aim of this study was to evaluate the prevalence of CMV infection among neonates who born in Vali-e-Asr hospital of Birjand located in Birjand city, over a one-year period and also assess the clinical outcomes of the disease in the neonates.

2- MATERIALS AND METHODS

2-1. Study design and population

In this cross-sectional study, 868 neonates were selected using unconditional random sampling during the year of 2017 (in twelve months) in Vali-e-Asr hospital of Birjand, South Khorasan province, Iran. The newborns born in the hospital were entered into the study without any restrictions (both term and preterm). The number of newborns with regards to CMV prevalence in developing countries with a p-value of P = 0.10, was determined by the following sample size formula and a 95% confidence level (CI).

$$n = \left(\frac{z\left(1 - \frac{a}{2}\right) p(1-p)}{d^2} \right) = 868$$

2-2. Methods

On the first or second day of birth, saliva sample was taken from neonates using a Dacron swab, where the swab was places on neonates' buccal mucosa until moist and the specimen was then placed into transport medium (tube containing 500 µl saline buffer), then transferred to the university's research center as soon as possible. The samples were rapidly shaken, and the resulting liquid was stored at -20 ℃ until the testing time. In the laboratory, DNA samples were extracted using a DNA extraction kit (Intron, Korea) in accordance with the manufacturer's instructions. The extracted samples were stored at -20ºC for a short time and then used for Polymerase chain reaction (PCR) and analysis with in the first 2 weeks of their life at most.

A real-time PCR protocol described by Boppana et al. (15), and Ross et al. (16) to detect CMV DNA in saliva samples. All samples were examined for possible CMV virus with PCR method, using a pair of external primers and a pair of internal nested PCRs in order to detect UL55 genes. The lower limit of detection by real-time PCR was 50 copies/ml for the saliva samples. Neonates with positive PCR (either symptomatic or asymptomatic) were fully examined and evaluated, and their developmental progression was re-assessed at 2 months, 4 months, and 6 months (full follow up period was 6 months). Neonates were placed in the symptomatic group and were examined for at least one of the following diseases was needed in order to be diagnosed with congenital CMV infection: Petechia, Purpura, Direct Bilirubinemia, Hepatosplenomegaly, Microsphere (round head circumference above three standard deviations below mean for age and gender), seizure, Chorioretinitis, brain ultrasound findings (including interstitial calcification, Ventriculomegaly, Atrophy or malformation), intrauterine growth retardation (embryo development curve 2, standard deviation below the mean curvature of gestational age), sensory neural hearing impairment based on auditory brainstem response (ABR), and auditory threshold of more than 15 dB, anemia (amount Hg in terms of age), liver function dysfunction (evaluation of PT and Alb values by age), blueberry muffin rash (papulonodular purple color) (17). Meanwhile, if the symptomatic patient was diagnosed with the Central Nervous System (CNS), he/she would be admitted at the Neonatal Intensive Care Unit (NICU), and treated with venous ganciclovir. In case any other symptom was present, check-up and treatment would start according to the specific problem.

2-3. Measuring

The study subjects were complete physically examined by podiatrist and pediatric resident. All infants were examined at the time of birth for complete height with an infantometer (made Iran, with an error of 0.5 cm), and weight measures as well as head circumference and the obtained data were recorded by pediatric resident. Weighing of the neonates by German Seca digital scale with 100 gr calibration weight was done.
The evolution process was performed using the Ages and Stages Questionnaire (ASQ) at the age of 4 (ASQ4), and 6 (ASQ6) months. The questionnaire included two parts: the first part included recording of demographic data (i.e. gestational age, patient's gender, type of symptoms, weight and height at birth). The second part included recording laboratory evaluations and information on follow-up evaluations using ASQ4 and ASQ6.

2.4-Ethical consideration

Ethical considerations in this study specified as following:

- Ethics approval was obtained from the Ethics Committee of the Birjand University of Medical Sciences (approved by the Ethics Committee: IR.BUMS.REC.1396.115),
- Full parental consent forms were signed by the parents,
- No charge for the infant's families,
- Infants were referred to a specialist for follow-up if diagnosed with any disease or disorder.

2-5. Inclusion and exclusion criteria

The entry criteria in this study were included:

- ❖ Any live birth at the Vali-e-Asr hospital of Birjand city,
- ❖ Full parental consent of the parents or legal guardian of the infant for participation in the study.

Infants were excluded if they did not meet the selection criteria above.

2-6. Laboratory measurements

For all infants with positive PCR, abdominal ultrasound (in terms of hepatocellular malignancy), and ophthalmic examination (for Chorioretinitis), and auditory examination was performed by ABR tests. The evaluation of brain disorders was performed by brain ultrasound and clinical examinations at the hospital that indicate seizure, microcephaly and developmental disorder. Biochemical parameters including CBC (Complete blood count) (WBC, NEUT, Hg, and PLT), AST, ALT, PT, Alb and Bil (D & T) tests were used to evaluate anemia, neutropenia and thrombocytopenia, as well as liver and jaundice dysfunction. The results of the said tests were evaluated based on Kliegman et al. (17), the normal values of the above parameters were considered as follows: WBC 6,000-14,000/µL, NEUT >1,500/µL, Hg 10-14 gr/dL, PLT 150-450*10^9/L, AST 22-63 u/L, ALT 12-45 u/L, PT 10.1-15.9 second, Alb 1.9-4.9 gr/dL, Bil T <1 mg/dl, and Bil D <0.5 mg/dl.

2-7. Data Analysis

Data were analyzed using SPSS software version 21.0 (IBM Corp. IBM SPSS Statistics for Windows). Mean, standard deviation and frequency distribution were separately used to describe the research sample. Next, quantitative variables of the normal distribution were determined by the Climograph-Smirnoff test (17). Chi-square test and Fisher's exact test were used for demographic data analysis. A p-level of <0.05 was considered statistically significant.

3- RESULTS

There were 868 live births in the Vali-e-Asr Hospital of Birjand in a span of twelve months of the study in 2017, of which the PCR test indicated positive results in 14 neonates (1.61%). Information about 2 cases of positive PCR cases were discarded due to parents' disagreement to continuation of the study. Of 868 neonates, 787 (90.67%) newborns were term and 81 births (9.33%) were preterm. None of the neonates with positive PCR were premature. There was no significant relationship between positive PCR and preterm labor (P = 0.10). The prevalence of CMV infection in term neonates was higher than that of preterm infants, although there was no statistically significant difference (**Table 1**). Of the 14 cases of PCR positive, 6 cases (42.85) were male and 8 cases (57.15) were female (**Figure.1**). There was no significant relationship between positive PCR and infant's gender (P = 0.09). None of the PCR-positive neonates had a clinical sign and/or symptom (P = 0.001). The height in PCR positive neonates ranged from 43 to 53 cm. The average height of neonates was 2.92 ± 50.21 cm, minimum height was

47.52, and maximum height was 50.90 cm. The mean of head circumference of neonates was 33.5 ± 1.68, the minimum head circumference diameter was 31.52, and the maximum head circumference was 33.47 cm. All PCR positive neonates fell in the normal weight range. However, there was no significant statistical difference between CMV infection and birth weight of the neonates (**Table.1**). Of the 14 neonates with PCR, only 1 infant was LBW (2325 g), and the rest had normal birth weight. There was no significant relationship between positive PCR and low birth weight (P = 0.93).

The data on demographic factors and initial evaluations are presented in **Table.1** and **Figure.1**. As shown in **Table.1**, the majority of neonates had normal weight, and only (12%) weighed less than 2500 g. 764 newborns had normal birth weight (88.47%), 93 cases (10.7%), LBW and 11 (1.26%) VLBWs (**Figure.1**). The mean of neonatal weight was 3083±492.5 g, the minimum weight was 2798 g, and the maximum weight was 3366 g. Information on PCR positive neonatal trials is presented in **Table.2**. No hearing loss the PCR positive neonates was reported. Hearing was normal in ABR group. Eye examination of PCR positive neonates indicated normal results. Brain and abdominal ultrasound of PCR positive neonates were all reported to be normal. No other clinical symptoms, including Seizure, Rashes, Peptic Ulcer, Purpura, Hepatosplenomegaly, were observed in any of the PCR positive infants (**Table.2**). Microcephaly was not present in any of the PCR positive neonate and head circumference was with in a normal range (mean = 33.5, standard deviation = 1.68).

Examinations indicated that none of the PCR positive neonates suffered from liver dysfunction, thrombocytopenia, bilirubin, and jaundice. Anemia was observed in 3 cases (25%) and neutropenia in 4 cases (33%). The most common abnormalities were symptoms of neutropenia (50% of symptoms) followed by anemia (37.5% of symptoms). During the study, none of the positive PCR neonates died. The ASQ score performed at four (ASQ4) and six months (ASQ6) in all positive PCR infants was within the normal range and above the standard deviation of the cut-off point (P=0.00).

Table-1: Comparison of anthropometric indices, birth weight, CMV infection, demographic characteristics and PCR positive frequency of neonates

a) Frequency of anthropometric indices			
Weight (g)	3017.49±528.72	Min	700
		Max	4645
Infant Head Circumference	33.97±2.38	Min	20
		Max	52.5
Height (cm)	49.35±3.98	Min	28
		Max	57
b) Frequency of birth weight of newborns		No. of Infants (%)	
Normal weight *		764 (88%)	
LBW*		93 (10.7%)	
VLBW*		11 (1.3%)	
c) Frequency of cytomegalovirus (CMV) infection			
	Positive CMV	Negative CMV	Statistical test
Term Infants	14 (1.61%)	773 (98.39%)	X^2=1.25, DF=1, P=0.30
Premature infants	0 (0)	81 (100%)	
Normal weight	13 (1.6%)	752 (98.4%)	Fisher exact =1.19 , P=0.68
LBW	1 (1.1%)	92 (98.9%)	
VLBW	0 (0)	11 (100%)	

d) Frequency of demographic characteristics and PCR positive infants (14 cases)			
PCR* results	Positive	14 (1.61%)	-
	Negative	854 (98.39%)	
Gender	Girl	8 (57.15%)	P=0.09
	Boy	6 (42.85%)	
Gestational age	Term	14 (100%)	
	Premature	0	
Birth weight	Normal weight	13 (92.86%)	P=0.93
	LBW	1 (7.14%)	
	VLBW	0	
Clinical symptom	Marked	0	-

CMV: Cytomegalovirus; *Normal weight: Weight greater than 2,500 gr; LBW: Low Birth Weight: 1,500-2500 gr; VLBW: Very Low Birth Weight: less than 1,500 gr; PCR: Polymerase chain reaction; DF: Degree of Freedom.

Table-2: Laboratory test results for 12 newborns out of 14 positive PCR*

Infants	WBC (10^3/µL)	NEUT (10^3/µL)	Hb (gr/dl)	PLT (10^9/L)	PT (Second)	INR	AST (u/lit)	ALT (u/lit)	Bil (mg/dl)		Alb (gr/dl)
									T	D	
1	7.4	9.2	11.6	397	13	1	51	34	0.9	0.3	3.9
2	7.7	6.7	10.6	710	12	0.9	24	22	0.5	0.1	3.8
3	12	30	8.4	388	12	1	38	37	0.7	0.2	2.5
4	6.7	15.8	10.7	435	13	1	26	21	0.6	0.1	4
5	15.6	31	10	591	13	1	21	25	1.1	0.3	4
6	14.7	47	9.7	704	12	0.9	33	22	0.3	0.1	3.7
7	11	50	10.7	878	13	1	40	17	0.4	0.1	3.5
8	8.2	33	11.2	634	13	1	41	30	0.5	0.2	3.5
9	7.6	7.5	10.8	561	13	1	48	46	0.5	0.2	3.8
10	10.9	18.7	10.9	441	13	1	38	40	0.3	0.1	3.9
11	11.6	42	9.9	350	12	1	38	32	0.9	0.4	3.5
12	9.8	31	10.1	274	13	1	38	25	0.4	0.2	3.6

Frequency of Clinical and Laboratory Symptoms of 12 Infants with positive PCR *

Symptoms	Numbers	Percentage (between positive PCRs)	Percentage (between symptoms)
Anemia	3	25	37.5
Neutropenia	4	33.3	50
Jaundice-Microcephaly-Hepatosplenomegaly-Seizure-Corythrinitis-Developmental Disorders-Brain Disorders-Thrombocytopenia-Death = **0 Cases**			

* Two infants were not tested due to the lack of parental consent, thus the number of samples in laboratory results was 12. WBC: White Blood Cells; NEUT: Neutrophils; Hb: Hemoglobin; PLT: Platelet number; PT: Prothrombin time; INR: The international normalized ratio; AST: The Aspartate Aminotransferase test; ALT: Alanine Aminotransferase test; Bil: Bilirubin (D: Direct Bilirubin, T: Total Bilirubin); Alb: albumin.

4- DISCUSSION

Based on the results of this study, of 868 neonates, 787 (90.67%) newborns were term and 81 births (9.33%) were preterm and the PCR test indicated positive results only in 14 term neonates (1.61%), and none of the neonates with positive PCR were preterm. The prevalence of congenital CMV in this study was shown to be 1.61%, which is parallel to other similar studies conducted in Brazil (18), China (19), Mexico (20), Japan (21), Korean (22), and Iran (Bushehr, Kerman, Golestan provinces) (23, 24, 25). The prevalence of congenital CMV in developed countries such as the Netherlands (26), Sweden (27), and Ireland (28) was below the prevalence in

our study prevalence. Meanwhile, congenital CMV prevalence in many developing countries with low health status, such as India (29), was higher compared to this study (3.8%). In terms of comparison within Iran, the prevalence of congenital CMV in this study was almost the same as the prevalence of similar studies in other cities in Iran (23-25). However, a research by Karimian et al. (30) in Isfahan- Iran, showed a lower prevalence (0.49%) compared to this study. Although congenital CMV infection is widespread throughout the world, the prevalence of congenital CMV infection among developing counties with lower health, economic, and social status is far higher than in developed countries with high economic, health, and social status (31). The common prevalence level is about 1 to 2.5% of all births, which is also affected by geographical area, race and socio-economic conditions of infants (31).

Moreover, the study of Hassan et al. (32) in Ireland has shown that geographical areas with the highest prevalence of this infection are Africa, Asia and South America and the lowest are found to be Western Europe and North America. None of the newborns with positive PCR were preterm. There was no significant relationship between positive PCR and preterm delivery ($P< 0.10$). The same results were found in the study of Wang et al. (19) in the developed region of China and Ivanov et al. (33) in Bulgaria. However, in Karimian et al. (30) study, the congenital CMV was associated with preterm birth. Of the 14 PCR positive infants, 6 (42.85%) were male and 8 (57.15%) were female and no significant relationship between PCR positive and neonatal gender was observed ($P< 0.05$). 33.3% of PCR positive babies were symptomatic, which is similar to the results of studies by Karimian et al. (30) and Ivanov et al. (33), have reported that none of the newborns were symptomatic at birth. Considering that all positive PCR samples were term, the comparison of symptomatology frequency of term neonates and preterm was not possible. None of the PCR infants had a sensory neural hearing loss in this study. These results were also found in the studies of Ivanov et al. (33) and Wang et al. (19). However, majority of studies in this field have reported sensory hearing loss to be the most common symptom and complication of congenital CMV complications (26, 27, 34), and all have emphasized that hearing loss could begin with a delay. Due to the absence of hearing loss, comparing hearing loss in newborns based on symptomatology was not possible. In terms of the ASQ score, no studies were found similar to this study.

However, several studies have examined the long-term effects of congenital CMV infection on hearing and child development, which showed that the chance of hearing impairment in childhood increases in positive PCR infants and congenital CMV causes of developmental disabilities (30, 35-38). Among all symptoms, the most common abnormalities were neutropenia (50% of symptoms) followed by anemia (37.5% of symptoms) which was similar results reported by Gandhoke et al. (29) in India.

The frequency of symptomatic neonates at birth in this study was higher than the average global range, but almost the same as in developing countries.

5- CONCLUSION

In this study, the congenital CMV was only observed among term neonates and its prevalence (1.61%) was in the range of common prevalence level in industrialized countries, and there was no association between CMV infection and birth weight, infant gender, and as well ae neonatal type. The symptoms presented in this study were mild and mostly in laboratory scale, while in most studies, more serious clinical

symptoms (hepatosplenomegaly, Seizures, microcephaly, hydrocephalus, etc.) were observed. Regarding the prevalence of congenital CMV, it seems that the attention and regular medical follow-up (in accordance with the global guidelines) of pregnant women in Birjand, has led to a decrease in the chances of obtaining congenital CMV in Birjand. However, congenital CMV infection yet remains as one of the most important health issues in both pregnant women and infants in Birjand. Thus, it is necessary to implement more and better strategies to reduce congenital CMV infection, including early screening of mothers or infants for early identification of symptoms and thus, better treatment of infected infants and mothers. In fact, the results of this study can be helpful in formulating a proper health plan in order to prevent the infection in pregnant mothers, and consequently prevent the fetus infection and complications associated with it.

6- ABBREVIATION

CBC: Complete Blood Count,
WBC: White Blood Cells,
NEUT: Neutrophils,
Hb: Hemoglobin,
PLT: Platelet number,
AST: Aspartate Aminotransferase Test,
ALT: Alanine Aminotransferase Test,
PT: Prothrombin Time,
Alb: Albumin,
Bil (D & T): Bilirubin (D: Direct Bilirubin, T: Total Bilirubin),
INR: The International Normalized Ratio.

7- CONFLICT OF INTEREST: None.

8- ACKNOWLEDGMENT

The authors express their gratitude to the research deputy of Birjand University of Medical Sciences. They would also like to thank the employees of the NICU of Vali-e-Asr Hospital in Birjand, and specially, we appreciate those who have participated in this research.

9- REFERENCES

1. Lanzieri TM, Dollard SC, Bialek SR, Grosse SD. Systematic review of the birth prevalence of congenital cytomegalovirus infection in developing countries. International Journal of Infectious Diseases. 2014; 22:44-8.

2. Imanzade F, Sayyari A, Tajik P. Cytomegalovirus Colitis in an Immunocompetent Patient: Report of a Case. International Journal of Pediatrics. 2015;3(2.1):85-8.

3. Marsico C, Kimberlin DW. Congenital Cytomegalovirus infection: advances and challenges in diagnosis, prevention and treatment. Italian journal of pediatrics. 2017; 43(1):38.

4. Janan A, Honarmand H, Amirmozafari N, Asgharnia M, Janan A. Study on seroprevalence of cytomegalovirus in pregnant women reffered to Mehr Institute and the association of cytomegalovirus seropositivity to spontaneous abortion. J Mazandaran Univ Med Sci. 2013; 23 (105):36-42.

5. Muldoon KM, Armstrong-Heimsoth A, Thomas J. Knowledge of congenital cytomegalovirus (cCMV) among physical and occupational therapists in the United States. PloS one. 2017; 12(10): e0185635.

6. Buxmann H, Hamprecht K, Meyer-Wittkopf M, Friese K. Primary human cytomegalovirus (HCMV) infection in pregnancy. Deutsches Ärzteblatt International. 2017; 114(4):45.

7. Munro SC, Hall B, Whybin LR, Leader L, Robertson P, Maine GT, et al. Diagnosis of and screening for cytomegalovirus infection in pregnant women. Journal of clinical microbiology. 2005; 43(9):4713-8.

8. Daley-Bauer LP, Roback LJ, Wynn GM, Mocarski ES. Cytomegalovirus hijacks CX3CR1hi patrolling monocytes as immune-privileged vehicles for dissemination in mice. Cell host & microbe. 2014; 15(3):351-62.

9. Carlson A, Norwitz ER, Stiller RJ. Cytomegalovirus infection in pregnancy: should all women be screened? Reviews in Obstetrics and Gynecology. 2010; 3(4):172.

10. Pass RF, Anderson B. Mother-to-child transmission of cytomegalovirus and prevention of congenital infection. Journal of the Pediatric Infectious Diseases Society. 2014; 3(suppl_1):2-6.

11. Lantos PM, Hoffman K, Permar SR, Jackson P, Hughes BL, Swamy GK. Geographic disparities in cytomegalovirus infection during pregnancy. Journal of the Pediatric Infectious Diseases Society. 2017; 6(3):55-61.

12. Wang C, Zhang X, Bialek S, Cannon MJ. Attribution of congenital cytomegalovirus infection to primary versus non-primary maternal infection. Clinical infectious diseases. 2011; 52(2):11-3.

13. Lim Y, Lyall H. Congenital cytomegalovirus–who, when, what-with and why to treat? Journal of Infection. 2017; 74: 89-94.

14. Amelia J, Nikunj M, William I, Shiu S. Congenital cytomegalovirus infection; Paeditric and child health. 2014; 24(6):255–259.

15. Boppana SB, Ross SA, Shimamura M, Palmer AL, Ahmed A, Michaels MG, et al. Saliva polymerase-chain-reaction assay for cytomegalovirus screening in newborns. New England Journal of Medicine. 2011; 364(22):2111-18.

16. Ross SA, Ahmed A, Palmer AL, Michaels MG, Sánchez PJ, Bernstein DI, et al. Detection of congenital cytomegalovirus infection by real-time polymerase chain reaction analysis of saliva or urine specimens. The Journal of infectious diseases. 2014; 210(9):1415-18.

17. Kliegman R, Stanton B, St Geme JW, Schor NF, Behrman RE. Nelson textbook of pediatrics. Philadelphia, Pennsylvania: Elsevier, 2016.

18. Miura CS, Miura E, Mombach AB, Cheskya M. The prevalence of congenital cytomegalovirus infection in newborn infants at an intensive care unit in a public hospital. Jornal de pediatria. 2006; 82(1):46-50.

19. Wang S, Wang T, Zhang W, Liu X, Wang X, Wang H, et al. Cohort study on maternal cytomegalovirus seroprevalence and prevalence and clinical manifestations of congenital infection in China. Medicine. 2017; 96(5): e6007.

20. Noyola DE, Mejía-Elizondo AR, Canseco-Lima JM, Allende-Carrera R, Hernández-Salinas AE, Ramírez-Zacarías JL. Congenital cytomegalovirus infection in San Luis Potosi, Mexico. The Pediatric infectious disease journal. 2003; 22(1):89-90.

21. Yamamoto A.Y. et al; Prevalence and clinical aspects of congenital cytomegalovirus infection; Jornal de Pediatria 1999, 75(1):23-8.

22. Sohn YM, Park KI, Lee C, Han DG, Lee WY. Congenital cytomegalovirus infection in Korean population with very high prevalence of maternal immunity. J Korean Med Sci 1992; 7: 47–51.

23. Sanjideh M, Naeimi S, Moradi Nasab M, Moradi R, Vahdat K. Cytomegalovirus infection in NICU admitted neonates in Boushehr. ISMJ. 2016; 18(6):1171-78.

24. Arabzadeh AM, Mosavat SA, Eftekhari N. Seroepidemiology of human cytomegalovirus in pregnant women and their neonates in Kerman city during 2005. Journal of Kerman University of Medical Sciences. 2014; 14(4):279-88.

25. Javid N, Cheraghali F, Moradi A, Kelishadi M, Tabarraei A. Newborn screening for congenital cytomegalovirus infection in Iran. The Pediatric infectious disease journal. 2016; 35(9):1052.

26. De Vries JJ, Korver AM, Verkerk PH, Rusman L, Claas EC, Loeber JG, et al. Congenital cytomegalovirus infection in the Netherlands: birth prevalence and risk factors. Journal of medical virology. 2011; 83(10):1777-82.

27. Engman ML, Malm G, Engström L, Petersson K, Karltorp E, Teär Fahnehjelm K, et al. Congenital CMV infection: prevalence in newborns and the impact on hearing deficit. Scandinavian journal of infectious diseases. 2008; 40(11-12):935-42.

28. Waters A, Jennings K, Fitzpatrick E, Coughlan S, Molloy EJ, De Gascun CF, et al.

29. Incidence of congenital cytomegalovirus infection in Ireland: implications for screening and diagnosis. Journal of clinical virology: the official publication of the Pan American Society for Clinical Virology. 2014; 59(3):156-60.

30. Gandhoke I, Aggarwal R, Lal S, Khare S. Congenital CMV infection in symptomatic infants in Delhi and surrounding areas. The Indian Journal of Pediatrics. 2006; 73(12):1095-97.

31. Karimian P, Yaghini O, Nasr Azadani H, Mohammadizadeh M, Arabzadeh SA, Adibi A, et al. Prevalence, characteristics, and one-year follow-up of congenital cytomegalovirus infection in Isfahan City, Iran. Interdisciplinary perspectives on infectious diseases. 2016; 2016: 7812106.

32. Kenneson A, Cannon MJ. Review and meta-analysis of the epidemiology of congenital cytomegalovirus (CMV) infection. Reviews in medical virology. 2007; 17(4):253-76.

33. Hassan J, O'neill D, Honari B, De Gascun C, Connell J, Keogan M, et al. Cytomegalovirus infection in Ireland: Seroprevalence, HLA class I alleles, and implications. Medicine. 2016; 95(6): e2735.

34. Vanov IS, Popov NI, Moshe RI, Terzieva DD, Stefanov RS, Panova MV, et al. Prevalence of cytomegalovirus infection in hospitalized infants. Folia medica. 2012; 54(4):45-52.

35. Turner KM, Lee HC, Boppana SB, Carlo WA, Randolph DA. Incidence and impact of CMV infection in very low birth weight infants. Pediatrics. 2014: peds-2013.

36. Goderis J, De Leenheer E, Smets K, Van Hoecke H, Keymeulen A, Dhooge I. Hearing loss and congenital CMV infection: a systematic review. Pediatrics. 2014: peds-2014.

37. Buonsenso D, Serranti D, Gargiullo L, Ceccarelli M, Ranno O, Valentini P. Congenital cytomegalovirus infection: current strategies and future perspectives. Eur Rev Med Pharmacol Sci. 2012; 16(7):919-35.

38. Nijman J, Mandemaker FS, Verboon-Maciolek MA, Aitken SC, van Loon AM, de Vries LS, Schuurman R. Genotype distribution, viral load and clinical characteristics of infants with postnatal or congenital cytomegalovirus infection. PLoS One. 2014; 9(9):e108018.

39. Boppana SB, Ross SA, Fowler KB. Congenital cytomegalovirus infection: clinical outcome. Clinical infectious diseases. 2013; 57(suppl_4):S178-81.