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Seroprevalence Of Congenital Cytomegalovirus Infection In Neonates

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Abstract:

CMV is a leading cause of congenital infections worldwide; it is the commonest non genetic cause of childhood hearing loss in the post rubella era and a significant cause of neurodevelopmental delay [1].

CMV infections are usually asymptomatic in immunocompetent hosts but can cause life-threatening complications in immunocompromised individuals. CMV infection is a major problem in patients with AIDS and other immune disorders, transplant recipients, individuals admitted to intensive-care units, and to some extent in elderly people. However, the highest disease burden is due to congenital CMV [2].

Aim of the study:

To estimate seroprevalence of congenital CMV in neonates and to evaluate its effect on neonates.

Patients and methods:

This study was performed in the NICUs of Fayoum university hospital and General hospital during the period from October 2018 to May 2019. A total number of 267 neonates were included in the study. All newborns were subjected to laboratory investigations including (CBC, ALT, AST, Serum bilirubin (total& direct), CMV IgM

and CMV IgG), then CMV PCR was done to positive CMV IgM neonates.

Results: Our study included a total number of 267 neonates less than 3 weeks old. To search for the seroprevalence of CMV among our patients,CMV IgM & IgG were performed (at a mean age of 10.5± 9.5 days). CMV IgM was found positive in 3 patients(1.1%) and CMV IgG was positive in all cases (100%).To confirm our results, CMV PCR was performed for the three patients with positive CMV IgM, which showed that two of them (0.7%) had a positive PCR too.

Conclusion: Congenital CMV infection is not as common in our neonates and may cause morbidity and mortality in neonates.

Keywords: congenital, cytomegalovirus, prevalence, infections, neonates

Introduction:

Human Cytomegalovirus (CMV) is a ubiquitous human-specific DNA virus, belonging to the Herpesviridae family [3].

Mother-to-child transmission of cytomegalovirus occurs transplacentally (congenital infection), during birth and through breast milk, although the latter 2 modes of transmission are not associated with the central nervous system sequelae that occur with congenital infection [4].

The prevalence of congenital CMV infection has been reported to vary from about 0.2% to 2% (average 0.65%), with higher overall rates in countries with higher maternal seroprevalence **(Khalil et al., 2018).** [5].

The clinical spectrum of congenital CMV infection varies widely, from asymptomatic infection to potentially life-threatening disseminated disease. At birth, 85–90% of infected infants are asymptomatic, and 10–15% present with symptomatic disease [3].

Subject and methods:

This study was performed in the NICUs of Fayoum university hospital and Fayoum General hospital during the period from October 2018 to May 2019.

Patient's selection:

A total number of 267 neonates were included in the study.

Inclusion criteria:

 All neonates less than 3 weeks old.

 Both males and females.

 All neonates either asymptomatic or symptomatic as neonates with organomegaly, respiratory distress, low birth weight, microcephally, neurological deficit or congenital anomalies. .

Exclusion criteria:

 Neonates more than 3 weeks old.

Methods: ***Neonates in the study were subjected to:***

1.Detailed history taking from the mother with emphasis on

 Maternal illness, maternal infections, maternal fever or rash during the pregnancy.

 History of previous abortions, stillbirths, congenital anomalies in previous siblings was recorded.

 History of obstructed labor

Gestational age, mode of delivery, age of presentation, birth weight and PROM.

 Historty of pallor, cyanosis, jaundice, seizures, abdominal distension or difficult breathing at birth.

2.***Thorough physical examination*** laying stress on

 Confirmation of gestational age with Ballard score assessment.

 Measurement of anthropometric parameters that were plotted on the Egyptian growth curves (weight, length and head circumference).

 Vital signs (heart rate, respiratory rate, temperature).

 Pallor, jaundice, cyanosis.

 Chest examination: (air entry, added sounds and respiratory distress).

 Cardiac examination :(heart sounds and murmur).

 Abdomen examination: (hepatomegaly, splenomegaly).

 Conscious level and seizures.

 Eyes examination and fundus when indicated.

 Abnormal features or congenital anomalies .

3: Laboratory evaluation:

All neonates were subjected to the following laboratory investigations.

 CBC&CRP.

 ALT, AST&serum bilirubin (total& direct).

 ABG& ABO,Rh if indicated clinically.

 CMV IgM &CMV IgG then CMV PCR was done to CMV IgM positive neonates.

Statistical analysis of data:

The collected data were organized, tabulated and statistically analyzed using SPSS software statistical computer package version 22 (SPSS Inc, USA). For quantitative data, the **mean** and **standard deviation (SD)** were calculated. **Student-t test** was used as a test of significance to compare between neonates with positive CMV IgM versus those with negative CMV IgM. Qualitative data were presented as **number** and **percentages**, **chi square (χ2)** or **Fisher's exact** test, when appropriate, was used as a test of significance. **Level of significance:** For all above mentioned statistical tests done, the threshold of significance is fixed at 5% level (P-value).

Results:

Demographic characteristics of the study population:

The age of our studied participants ranged between 1 and 20 days with a mean age of 10.5±9.5 days. Regarding sex, more than half (56.6%) were males. As for gestational age, about 76.2% were fullterm, nearterm neonates were 8.9% and preterm neonates were 14.9%. For birh weight, the majority of cases were AGA 93.2%, 1.9% was SGA and 4.9% were LGA. As shown in table 1.

To search for the seroprevalence of CMV among our patients, CMV IgM & IgG were performed (at a mean age of 10.5± 9.5 days). CMV IgM was found positive in3 patients(1.1%) and CMV IgG was positive in all cases (100%).To confirm our results, CMV PCR was performed for the three patients with positive CMV IgM, which showed that two of them had a positive PCR too as shown in figure 1.

SGA was more prevalent among patients with positive CMV IgM than those with negative CMV IgM (P-value< 0.05). Prematurity was more prevalent among positive CMV IgM (33.3%) than negative CMV IgM neonates (14.8%) as shown in table 2.

positive CMV IgM cases have a higher percentage of microcephaly & IUGR with significant difference (P – Value< 0.05) as shown in figure 2.

There is no significant difference between positive CMV IgM and negative CMV IgM cases regarding prenatal risk factors and no risk factors were found in positive CMV neonates as shown in table 3.

Jaundice, cyanosis, pallor and HSM were observed more frequently in CMV positive cases than negative ones (66.7% Vs 39.4%, 33.3% Vs 31.8%, 33.3% Vs 19.3%, 33.3% Vs 26.9% and 33.3% Vs 7.2%),however the difference was not stastically difference as shown in table 4

Anemia, thrombocytopenia, elevated transaminases and cholestasis were observed more frequent among positive CMV IgM

cases than negative ones; however the difference was not stastically difference as shown in table 5.

Discussion:

Congenital CMV infection is defined as infection which is transmitted tranplacental from the mother to the fetus during maternal viremia [6], also perinatal transmission can occur through ingestion or aspiration of cervico-vaginal secretions at time of delivery [7].

The definitive diagnosis of congenital CMV infection is made by finding one or more of the following on a specimen collected from the infant in the first three weeks of life: isolation of virus from the urine or other secretions such as saliva, detection of CMV-specific IgM in the blood, and/or detection of CMV DNA by polymerase chain reaction in the urine, blood, saliva or other secretion. While a positive result on any of these tests after the first three weeks of age is also consistent with congenital CMV infection, the possibility of CMV acquired at birth or in the postnatal period cannot be excluded after this time period as the incubation period of the virus is about three weeks [8].

According to our study, seroprevalence of congenital CMV was found 0.7% of our neonates, this is in accordance with the data of a study from Egypt by **Abdel Hamid et al., (2011)** which found that the prevalence of congenital CMV was 1.28% (2 cases in 178 neonates less than 2 weeks old) but this study used the viral culture method to detect CMV in urine specimens[9].

However, the worldwide prevalence of congenital CMV infection has been reported to vary from about 0.2% to 2% (average 0.65%) [5].

In our study, our symptomatic case had microcephaly, HSM, thrombocytopenia, elevated transaminases, and cholestasis. A study by **Kylat et al., (2006)** found that common findings at presentation for symptomatic congenital CMV were hepatosplenomegaly 45%, microcephaly 37%, thrombocytopenia 50%, elevated transaminases 50% and cholestasis 50% [10].

In our study one with positive CMV PCR was preterm and the second case was a fullterm. A study in Iran enrolled 1617 neonates found 8 of them to have congenital CMV, two cases were preterm and six were full term [11].**.** Also in a study by **wang et al., (2017)** congenital CMV infection was twice as prevalent among preterm infants as full term infants (1.3% vs. 0.6%) [12].

In our study the prevalence of CMV IgG in our patients was 100%. IgG antibodies are mostly maternally transferred antibodies indicating maternal CMV seroprevalence [13].

The same results were reported in an Egyptian study involving 546 pregnant women , all (100%) were seropositive for anti-CMV IgG [14].

Conclusion: Congenital CMV is not as common in our cases but, it may lead to morbidity and mortality in neonates. Also, congenital CMV infection may be asymptomatic at birth. History of maternal fever or skin rash is not necessarily to be present in congenital CMV infection. CMV IgM test is a good test for congenital CMV screening in neonates but needs to be confirmed by CMV PCR test.

Reference:

1. Manicklal S, Emery VC, Lazzarotto T et al. The "silent" global burden of congenital cytomegalovirus. *Clin Microbiol Rev*. 2013; 26(1):86–102
2. Lachmann R, Loenenbach A, Waterboer T *et al*. Cytomegalovirus (CMV) seroprevalence in the adult population of Germany. PLoS ONE. 2018; 13(7): e0200267
3. Marsico C and Kimberlin DW. Congenital Cytomegalovirus infection: advances and challenges in diagnosis, prevention and treatment. *Ital J Pediatr*. 2017;43(1):38.
4. **Pass R.F. & Anderson B. :** Mother-to-Child Transmission of Cytomegalovirus and Prevention of Congenital Infection**.** *Journal of the Pediatric Infectious Diseases Society*, Volume 3, Issue suppl_1, 1 September 2014, Pages S2–S6
5. Khalil A, Heath P, Jones C, et al. Congenital Cytomegalovirus Infection: Update on Treatment. Scientific Impact Paper No. 56. BJOG 2018;125:e1–e11.
6. Syggelou A, Iacovidou N, Kloudas S et al. Congenital cytomegalovirus

infection. Ann. N.Y. Acad. Sci. 2010;1205 : 144–147 c

7. Navti O, Hughes BL, Tang JW, Konje J. Comprehensive review and update of cytomegalovirus infection in pregnancy. The Obstetrician & Gynaecologist 2016;18:301–7.

8. Waters A, Jennings K, Fitzpatrick E, et al. Incidence of congenital cytomegalovirus infection in Ireland: implications for screening and diagnosis.*J Clin Virol*. 2014;59:156–160

9. Abdel Hamid S, Abdel-Wahab S, Saleh L et al. Comparative Epidemiology of Infection with Human Cytomegalovirus in Cairo and South London. nternational Journal of Virology 2011;7(3): 116-122.

10. Kylat RI, Kelly EN and Ford-Jones EL. Clinical findings and adverse outcome in neonates with symptomatic congenital cytomegalovirus (SCCMV) infection. European Journal of Pediatrics. 2006 ;165(11): 773–778.

11. Karimian P, Yaghini O, Nasr Azadani H, 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

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

13. Nasir IA, Babayo A, Shehu MS. Clinical Significance of IgG Avidity Testing and Other Considerations in the Diagnosis of Congenital Cytomegalovirus Infection: A Review Update. *Med Sci (Basel)*. 2016; 4(1):5.

14. Kamel N, Metwally L, Gomaa N et al. Primary Cytomegalovirus Infection in Pregnant Egyptian

Women Confirmed by Cytomegalovirus IgG Avidity Testing. Med Princ Pract 2014;23:29–33

Table 1: Socio-demographic characteristics of studied group (N=267)

	Mean	**±SD**
Age at time of screening (days)	10.5	9.5
	N	**%**
Male	151	56.6
Female	116	43.4
Fullterm	203	76.2
Near term	24	8.9
Preterm	40	14.9
SGA	5	1.9%
AGA	249	93.2%
LGA	13	4.9%

Table (2): Comparison of demographic features among CMV IgM positive and negative patients

Variable	**Positive IgM (N=3)**		**Negative IgM (N=264)**		**P-value**
	Mean	**SD**	**Mean**	**SD**	

Age at time of screening (days)	**3**	**1.7**	**4.9**	**5.4**	**0.553**
Variable	**N**	**%**	**N**	**%**	**P-value**
Male	**2**	**66.7%**	**150**	**56.8%**	**1.000**
Female	**1**	**33.3%**	**114**	**43.2%**	
Fullterm	**2**	**66.7%**	**201**	**76.1%**	**0.609**
Near term	**0**	**0.0%**	**24**	**9.1%**	
Preterm	**1**	**33.3%**	**39**	**14.8%**	
SGA	**1**	**33.3%**	**4**	**1.5%**	**<0.0001***
AGA	**2**	**66.7%**	**247**	**93.6%**	
LGA	**0**	**0.0%**	**13**	**4.9%**	

Table (3): Comparison of Prenatal and natal risk factors among positive CMV IgM and negative neonates

Variable	**Positive IgM (N=3)**		**Negative IgM (N=264)**		**P-value**
	N	**%**	**N**	**%**	
Maternal fever	**0**	**0.0%**	**27**	**10.2%**	**1.000**
Maternal DM	**0**	**0.0%**	**20**	**7.6%**	**1.000**
Maternal HTN	**0**	**0.0%**	**12**	**4.5%**	**1.000**
Maternal rash	**0**	**0.0%**	**15**	**5.7%**	**1.000**

Drug intake	**0**	**0.0%**	**39**	**14.8%**	**1.000**
Similar conditions	**0**	**0.0%**	**32**	**12.1%**	**1.000**
CS delivery	**3**	**0.0%**	**190**	**72.0%**	**0.752**
Vaginal delivery	**0**	**0.0%**	**74**	**28%**	
PROM	**0**	**0.0%**	**44**	**16.7%**	**1.00**
Previous abortion	**0**	**0.0%**	**55**	**20.8%**	**0.988**

(4): Comparison of general examination between positive CMV IgM and negative neonates

Variable	**Positive IgM (N=3)**		**Negative IgM (N=264)**		**P-value**
	N	**%**	**N**	**%**	
Jaundice	**2**	**66.7%**	**104**	**39.4%**	**0.694**
Cyanosis	**1**	**33.3%**	**84**	**31.8%**	**1.000**
Pallor	**1**	**33.3%**	**51**	**19.3%**	**0.959**
Hepatomegaly	**1**	**33.3%**	**71**	**26.9%**	**1.000**
Splenomegaly	**1**	**33.3%**	**19**	**7.2%**	**0.418**
Petechial &	**1**	**33.3%**	**13**	**4.9%**	**0.299**

ecchymosis					
Abnormal eyes examination	**0**	**0.0%**	**8**	**3.0%**	**1.000**
Skeletal anomalies	**0**	**0.0%**	**7**	**2.7%**	**1.000**
Dysmorphic features	**0**	**0.0%**	**5**	**1.9%**	**1.000**

Table (5): Comparison of laboratory parameters among positive IgM CMV and negative neonates

Variable	**Positive IgM (N=3)**		**Negative IgM (N=264)**		**P-value**
	N	**%**	**N**	**%**	
Anemia	**1**	**33.3%**	**43**	**16.3%**	**0.837**
Thrombocytopenia	**1**	**33.3%**	**18**	**6.8%**	**0.399**
Leucopenia	**0**	**0.0%**	**5**	**1.9%**	**1.000**
Elevated Transaminases	**1**	**33.3%**	**57**	**21.6%**	**1.000**
Indirect hyperbilirubinemia	**2**	**66.7%**	**93**	**35.2%**	**0.578**
Cholestasis	**1**	**33.3%**	**17**	**6.4%**	**0.379**
Elevated CRP	**1**	**33.3%**	**109**	**41.3%**	**1.000**
ABO icompatibility	**0**	**0.0%**	**30**	**11.4%**	**1.000**
Rh incompatibility	**0**	**0.0%**	**5**	**1.9%**	**1.000**
Metabolic acidosis	**0**	**0.0%**	**80**	**30.3%**	**1.000**

Resoiratory acidosis	**1**	**33.3%**	**28**	**10.6%**	**0.585**

Figure (1): prevalence of CMV in neonates congenital

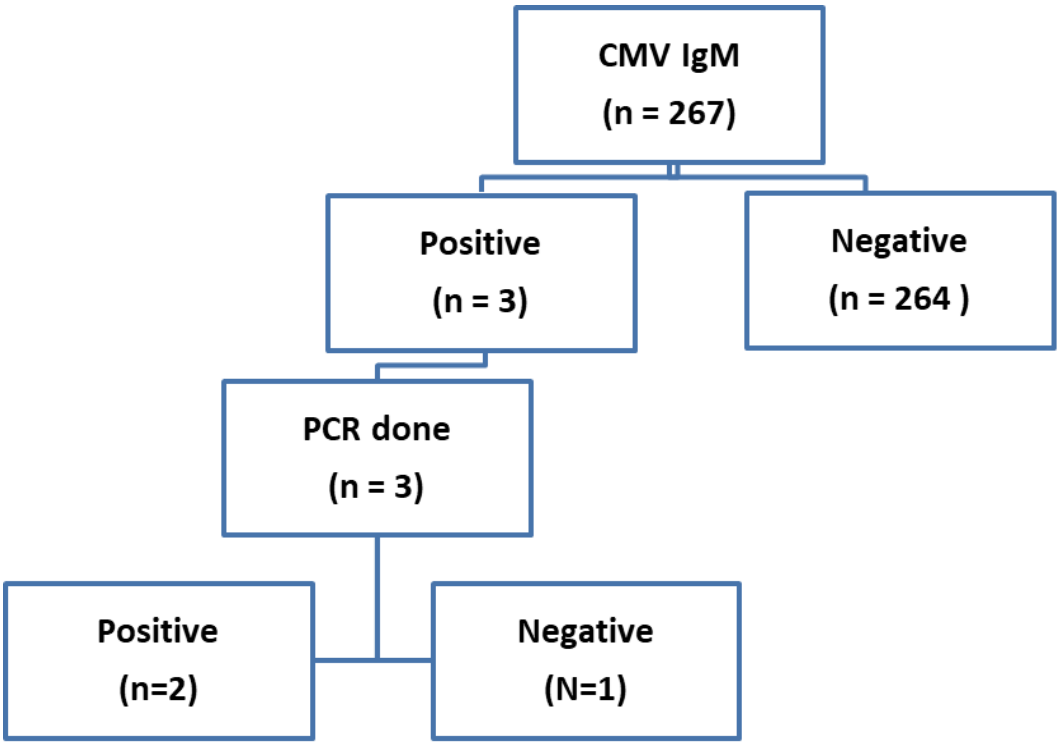
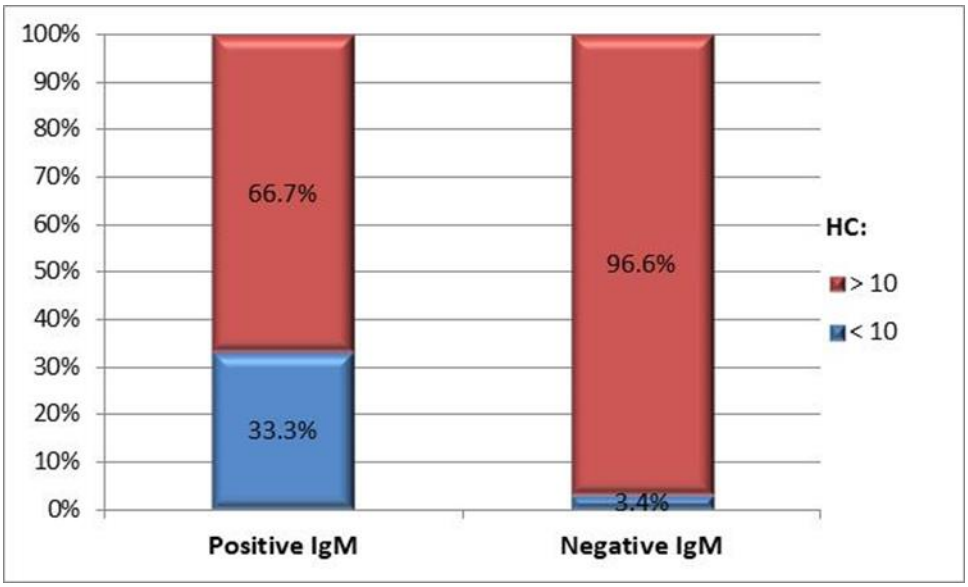


Figure 2: Head circumference in positive and negative IgM neonates


100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
66.7%
33.3%
96.6%
3.4%
HC:
> 10
< 10
Positive IgM
Negative IgM