Curr Pediatr Res2021; 25 (9): 929-935 *ISSN 0971-9032*
www.currentpediatrics.com

Impact of cytomegalovirus infection as a cause of Sensorineural Hearing Loss (SNHL) in children of Basrah, Southern Iraq.

Ahmed Hameed Hasan[1*], Hassan J Hasony[2], Ahmad M Al-Abbasi[3], Samer S Aziz4, Jaleel Samanje5

[1]Department of Microbiology, Basrah Medical College, Baghdad, Iraq

[2]Department of Microbiology, Basrah Medical College, Baghdad, Iraq

[3]Department of Surgery, Basrah Medical College, Baghdad, Iraq

[4]Department of Microbiology, Basrah Auditory Screening Center, Baghdad, Iraq

[5]Department of Health and Medical Technology, Middle Technical University, Baghdad, Iraq

Abstract

Background: The burden of CMV-associated Sensorineural Hearing Loss (SNHL) in populations with CMV seroprevalence approaching 100% is unknown. The purpose of this study was to assess the rate, associated factors and predictors of SNHL in CMV-infected infants identified by newborn screening in a highly seropositive maternal population.

Methods: Newborns with positive anti-CMV-Ab and confirmed by auditory assessment were enrolled in a prospective study to monitor the impact of CMV infection on hearing outcome using anti-CMV-IgG avidity and quantitative Polymerase Chain Reaction (qPCR).

Results: Hearing functions were assessed in 357 children who underwent at least one Auditory Brainstem Response (ABR) testing. SNHL was observed in 60/357 (16.8%) children of 1-10 years of age during 1st of Dec 2020 to mid of March 2021 at the latest hearing evaluation. Profound loss (>90 dB) was found in 75.4% children among them 81% with bilateral SNHL while all 2 children with unilateral loss had moderate to severe deficit. The presence of CMV infection detected in 80% of SNHL and in 8.3% of control group. Anti-CMV-IgG avidity was with high Avidity Index (AI) among 76.7% and low AI in 3.3% indicating non-primary CMV infections were the dominant. The correlation of CMV IgG avidity test for all (60) cases with SNHL disease, reveals a weak positive correlation value with (r=0.138) as more predictive and acceptable test for screening and diagnosis of child with CMV infection and the degree of SNHL disease, while the correlation of viral load (rt PCR-DNA) test for all (60) cases with SNHL disease showed a weak negative correlation with (r=-0.246), as the rt PCR is not predictive test for screening of CMV infection and degree of SNHL disease because the shedding of the virus in body fluid may be absent in latent stage of infection and not associated with anti-CMV-IgG low avidity index .

Conclusion: Even in populations with near universal immunity to CMV, congenital CMV infection is a significant cause of SNHL demonstrating the importance of CMV as a major cause of non-genetic SNHL in children, Anti-CMV-IgG Avidity Index (AI) is more predictive and acceptable test for screening and diagnosis of child with CMV infection and the degree of SNHL disease.

Keywords: Newborns, Neurodevelopmental abnormalities, Pure tone audiometry, Sensory deafness.

Accepted on 15th September, 2021

Introduction

Congenital CMV (cCMV) infection remains largely unrecognized in the developed and developing world although congenital CMV is now the leading infectious cause of Sensori Neural Hearing Loss (SNHL) and neurodevelopmental abnormalities in infants born in developed countries and second after cerebral palsy malformation in many parts of the world [1,2]. The risk of intrauterine transmission is highest when primary infection occurs during pregnancy, with a higher rate of vertical transmission in mothers with older gestational age at infection, while the risk of adverse fetal effects significantly increases if fetal infection occurs during the first half of pregnancy.

Several factors contribute to mortality and morbidity due to congenital CMV, including limited awareness of clinicians and parents about infections during pregnancy, low levels of routine check-ups for high-risk neonates, absence of maternal or neonatal screening programs, limited efficacy and toxicity of current treatments, and absence of licensed vaccines. In part, because of these limitations, congenital CMV and preventive measures for CMV acquisition during pregnancy are not routinely or consistently discussed with pregnant women or women trying to become pregnant [3]. The purpose of this study is to assess the rate, associated factors and predictors of SNHL in CMV-infected infants identified by newborn screening in a highly seropositive maternal population [4].

Materials and Methods

The referral Albasrah audiology center carried out the audiometric assessment for 357 children of 1-10 years old, during the period from Dec 2020 to March 2021 Pure Tone Audiometry (PTA), Auditory Brainstem Response utilizing clicks (ABR), or both were used in the audiometric examination.

Sixty children were diagnosed as Sensory-Neuronal Hearing Loss (SNHL) out of 357 examined children (16.8%). SNHL severity categorized for each ear using the ABR, according to the World Health Organization's standard categorization. Hearing loss can be classified as mild (26-40 dB), moderate (41-60 dB), severe (61-80 dB), or profound (81 dB or higher). All children submitted to an otological examination by an Ear, Nose, and Throat (ENT) specialist.

Sample collection of blood and processing

Five ml of a venous blood was drawn, and let stand for one hour at room temperature allowed to clot and then centrifuged at 3000 rpm for 5 minutes, serum sample was subdivided into two parts and emptied into sterile Eppendorf tube with the identification code, one for serological examination of HCMV IgG antibody and the other for HCMV IgG antibody avidity test.

Saliva sample collection for CMV DNA detection

Instructions for patient to clean their mouth 30 minutes before collecting the saliva sample rotating the tongue in the mouth to enrich saliva. Saliva delivered into the collection funnel, until the 2 ml line as instructed on the tube, both serum sample and saliva sample kept frozen at -20°C until time of examination.

IgG avidity

The TGS TA CMV IgG avidity test is a Chemiluminescent (CLIA) test that detects the presence of CMV IgG avidity for distinguish high avidity antibodies from low avidity antibodies allows for the provision of useful clinical information. The TGS TA CMV IgG avidity kit uses an indirect two-step immunological approach based on the concept of Chemiluminescence (CLIA) to determine the avidity index of only samples that have already been evaluated for the presence of IgG against CMV can be used in the test. An anti-human IgG antibody is labelled with an acridinium ester derivative, and the particular antigen is employed to coat the magnetic particles (solid phase) (conjugate).

Activation of the chemiluminescence process and measurement of the light signal (RLU) are used to determine the amount of labelled conjugate that stays attached to the solid phase, which indicates the amount of particular antibodies present in the sample, calibrators, and controls. The index of avidity of the anti CMV IgG present in the sample is the ratio between the concentration of antibodies in the second cuvette (treated sample-IgG not removed) and the concentration of antibodies in the first cuvette (not treated sample-total IgG). The avidity index of ≤ 0.15 considered at low avidity anti-CMV IgG, >0.15-0.20 considered at moderate and avidity of anti-CMV IgG>0.20 is considered at high avidity anti-CMV-IgG.

Results

Table 1 shows study population cases and the considered variables. Sixty cases of SNHL out of 357 referred children (16.8%) of 1-10 years during 3 months. Male gender is dominant (61.7% *vs*. 38.3%), and the majority of sensory deafness among cases (96.7%) of bilateral type and very few cases with unilateral type (3.3%). The degree of hearing damage as justified by ABR and PTA is mostly of sever profound type (68.3%) compared to moderate sever (31.7%) type. The majority of enrolled cases come from rural areas (63.3%) in comparison to urban areas (36.7%). However, 30% of cases diagnosed at early age group of 1-3 years, and 31.7% detected at age of 4-6 years which showed mild symptoms then increased at follow-up and 38.3% was detected at late age group of 7-10 years mostly asymptomatic cases.

Characters and variables		**Numbers (%)**
Gender	Male	37 (61.7%)
	Female	23 (38.3%)
Sensory deafness	Bilateral	58 (96.7%)
	Unilateral	2 (3.3%)
Degree of damage	Sever-profound	41 (68.3%)
	Moderate-sever	19 (31.7%)
Residency	Urban	22 (36.7%)
	Rural	38 (63.3%)
Age groups (Years)	(1-3)	18 (30.0%)
	(4-6)	19 (31.7%)
	(7-10)	23 (38.3%)

Table 1. Study population characteristics of SNHL diagnosed patients.

Table 2 shows the seroprevalence of CMV among the study population. Cases with SNHL associated with higher prevalence of anti-CMV-IgG (80%) compared to control group (8.3%). The differences is statistically significant (P<0.001).

Anti-CMV-IgG		**Total**		
Cases	**Control**			
	Negative	12	55	67
CMV		20.00%	91.70%	55.80%
	Positive	48	5	53
		80.00%	8.30%	44.20%
Total		60/357	60	120
		16.80%	100.00%	100.00%

Table 2. Seroprevalence of anti-CMV-IgG among SNHL cases and control group.

Total of 60 SNHL cases as justified by ABR and PTA hearing test showed that 47 (81%) positive for CMV- IgG with bilateral SNHL while only 1 (2.1%) positive for CMV- IgG antibody with unilateral SNHL (Table 3). The differences for the type of SNHL was statistically significant (P<0.05). On the other hand, 12 (20%) negative for CMV IgG who had SNHL for other reason not associated with CMV had 19% bilateral SNHL and (3.3%) unilateral SNHL, no significant difference between those with CMV seropositivity and those without CMV (p>0.05).

		Anti-CMV		Total
		Negative	Positive	
Sensory deafness	Bilateral	11	47	58
		19%	81%	96.70%
	Unilateral	1	1	2
		50%	50%	3.30%
Total		12	48	60
		20.00%	80.00%	100.00%

Table 3. SNHL type as tested by ABR and PTA and CMV-antibody.

The distribution of anti-CMV seropositivity in relation to previous history of jaundice, Seizures, abortion and family history of SNHL shows that it have no effects of CMV seropositivity among cases although the rates of anti-CMV antibodies was high (80%)in SNHL patients (P>0.05) (Table 4). There were no significant differences in CMV seropositivity between SNHL patients with postnatal history (79.4%) and those with no history (80.8%) of jaundice (P>0.05). However, all 6 patients with history of postnatal seizures were CMV seropositive (100%) with no significant differences from those with no history, even when proportion was low (10%) from the total SNHL cases, Patients with family history of abortion showed 68.2% seropositive to CMV, while anti-CMV rate was greater among those with no history of abortion (86.6%) There were, no significant difference in both (P>0.05). Family history of SNHL was found in 53.3% of patients; CMV positive antibodies detected in 84.4% of cases and in 75% of those with no family history of SNHL (P>0.05).

Presence		CMV antibody		Total
		Negative	Positive	
Jaundice	Yes	7 (20.6%)	27(79.4%)	34 (56.7%)
	No	5 (19.2%)	21 (80.8%)	26 (43.3%)
Seizures	Yes	0	6 (100%)	6 (10%)

	No	12 (22.2%)	42 (77.8%)	54 (90%)
Abortion	Yes	7 (15.6%)	15 (68.2%)	22 (36.7%)
	No	5 (13.2%)	33 (86.8%)	38 (63.3%)
Family history	Yes	5 (15.6%)	27 (84.4%)	32 (53.3%)
Of SNHL	No	7 (25%)	21 (75%)	28 (46.7%)
Total		12 (20%)	48 (80%)	60 (100%)

Table 4. Anti-CMV seropositivity in relation to clinical history.

Total cases enrolled for ABR and PTA hearing test with SNHL is presented in Table 5 show that there were no significant differences among those CMV-IgG positive (75.6%) who have sever-profound sensory SNHL compared to those with moderate-sever showed CMV seropositivity rate (89.5%) (P>0.05). In general the majority of SNHL cases had high damage degree (severe-profound) represent 68.3% of SNHL and 31.7% with moderate-sever SNHL, with marginal difference (P not attend<0.05).

		Anti-CMV		**Total**
		Negative	**Positive**	
Damage degree	Severe-profound	10	31	41
		24.40%	75.60%	68.30%
	Moderate-severe	2	17	19
		10.50%	89.50%	31.70%
Total		12	48	60
		20.00%	80.00%	100.00%

Table 5. Damage degree of SNHL (ABR and PTA test) and CMV positivity.

The majority of SNHL patients presented with high antibody avidity accounted for 76.7% indicating old and progressing type of CMV infections and few cases showed low antibody avidity which is possibly a recent infection or reactivation of latent CMV infection. However, the high antibody avidity distributed almost at the same rates among different age groups (P>0.05) although the high avidity slightly increased with increased age (Table 6).

Ages (years)		**IgG (UA/ml) avidity**			**Total**	**P-value**
		≤ 0.15 low	**>0.2 high**	**0 (Nul)**		
(1-3)	N	1	12	5	18	-0.7
	%	1.70%	20.00%	8.30%	30.00%	
(4-6)	N	0	16	3	19	
	%	0.00%	26.70%	5.00%	31.70%	
(7-10)	N	1	18	4	23	
	%	1.70%	30.00%	6.70%	38.30%	
Total	N	2	46	12	60	
	%	3.30%	76.70%	20.00%	100.00%	

Table 6. Distribution of IgG antibodies avidity among CMV cases according to age.

The distribution of positive viral load (CMV-DNA copies) in relation to type of SNHL disease, presented in Table 7. Positive viral load was detected among 18.3% of SNHL cases of whom 90.9% were with bilateral type of SNHL compared to 9.1% with unilateral type, all with anti-CMV IgG high avidity except one (9.1%) with low avidity. The difference between types is statistically significant (P<0.05).

Sensory deafness		Real time PCR results		Total	P-value
		Positive	Negative		
Bilateral	N	10	48	58	0.3
	%	90.90%	97.90%	96.70%	N.S
Unilateral	N	1	1	2	
	%	9.10%	2.10%	3.30%	
Total	N	11	49	60	
	%	18.30%	81.70%	100.00%	

Table 7. Distribution of CMV viral load (qPCR) according to type deafness.

In Table 8 shows the correlation of CMV IgG avidity test for all 60 cases with SNHL disease, a weak positive correlation value with 0.138 as more predictive and acceptable test for screening and diagnosis of child with CMV infection and the degree of SNHL disease, while the correlation of rtPCR test for all 60 cases with SNHL disease found a weak negative correlation with -0.246, as the rtPCR is not predictive test for screening of CMV infection and degree of SNHL disease because the shedding of the virus in body fluid may be absent in latent stage of infection and not associated with anti-CMV-IgG low avidity index.

Variable			**SNHL**	**Interpretation**	
Avidity IgG	Spearman's rho		0.138 (weak positive correlation)	Weak positive	
	P-value		0.292 (N.S)		
	N		60		
Variable			SNHL	RT-PCR	Interpretation
RT-PCR		Spearman's rho	- o.152 (weak negative correlation)	1	Weak negative
		P-value	o.246 (N.S)	-0.00	
		N	60	60	

Table 8. Correlation between the CMV IgG and rtPCR with SNHL degree.

Discussion

Congenital CMV infection has a wide clinical spectrum, ranging from total lack of symptoms (asymptomatic infection) to potentially life-threatening disseminated illness. Global estimates of cCMV incidence vary from 0.2% to 2%, with recent large studies being just under 0.5% [5]. The incidence of asymptomatic CMV infections and resulting SNHL may be higher, making it the leading cause of non-genetic SNHL in children, and because they develop later, both delayed and progressive hearing loss frequently remain undiagnosed during universal Newborn Screening (NHS) tests, so combined neonatal screening for CMV infection and repeated auditory evaluation will permit early identification of infants who at risk of CMV infection for purpose of targeted monitoring and intervention during critical stages of speech and language development. However, testing children diagnosed as SNHL for CMV infections revealed that 80% of SNHL cases positive for CMV IgG antibody compared to only 8.3% among control group which is higher than that reported by others [3,5]. These data from this study indicate that affected infants born to mothers with pre-existing immunity contribute significantly to CMV-related SNHL, despite the lower severity of the hearing loss. This is likely that the majority of children infected with CMV in this region will be born to mothers who have been previously exposed to CMV. Therefore, we believe that our data provides reliable estimates of CMV-associated SNHL in a highly seropositive population and suggests that current strategies to prevent morbidity associated with congenital CMV infection including the development of prophylactic vaccines to prevent primary maternal infections during pregnancy may have limited efficacy in the population.

About 85%–90% of infected newborns are asymptomatic at birth, whereas 10%–15% have clinically evident infection (symptomatic illness) [6,7]. Hearing loss may be evident at birth or develop later in the course of CMV-related SNHL; Late-onset SNHL affects newborns throughout their first few years of life, which is almost consistent with the trend observed in this study as the dominants were with high CMV-IgG avidity. Approximately half of children with SNHL experience continued worsening or progression of their hearing loss through childhood [8]. As a result, regardless of their

clinical presentation at birth, all newborns with congenital CMV infection should have serial audio logical monitoring during their first years of life to enable for early diagnosis of probable SNHL where large number of studied children with SNHL, detected at early age. Even if no particular pharmaceutical therapy is available for children who acquire CMV-related SNHL, early detection and non-pharmacological therapies can dramatically improve the infected child's receptive and expressive language, as well as their social-emotional development [9,10].

In 2013, the Paris group conducted a systematic study of Vidas AI (Avidity Index) values using well-defined sera they suggested that an AI of <40% be defined as low avidity and that an AI (Avidity Index) of >65% be defined as high avidity. These interpretive criteria have now been adopted by the manufacturer (bioMerieux) [11].

Maternal antibodies have been shown to penetrate the maternal-fetal membrane successfully, providing passive immunity against illnesses. Antibodies, on the other hand, may make it easier for CMV to get through the placenta barrier. CMV has been found to traverse the placenta as IgG-virion complexes via transcytosis using the Neonatal Fc Receptor (FcRn), which is present on the surface of syncytiotrophoblasts [12]. On the fetal side, high-avidity neutralizing antibody complexes are thought to be swiftly destroyed by villus core macrophages, but low-avidity antibody complexes allow virus to escape the macrophages and infect the fetus [13]. As a result, in this model, the timing of infection in relation to the onset of pregnancy, as well as antibody avidity to CMV, is important factors of protection. Low-avidity antibodies can last up to 20 weeks after a first infection [14]. This might indicate a high-risk period.

However, Passive CMV antibody injection in the postnatal era had no effect on the development of some neurological squealed, including progressive hearing loss, in the setting of congenital CMV infection [15]. Antibodies main benefit may be its ability to block transplacental transfer among children born with congenital CMV infection and whose mothers had a primary infection during pregnancy, 15% developed SNHL, and about 50% of them have bilateral SNHL [16] in contrast to the observed finding in this study where the majority of bilateral type of hearing loss. While Yamamoto et al. In 2011 in their predominantly CMV community reported that 33% of children infected with CMV after primary infection from mothers had SNHL and that all of their hearing loss was of a bilateral nature [17] where the percent in this study was higher. Hearing function should be evaluated at least annually until the age of 5-6 years [18] approximately 50% of children with SNHL after congenital CMV infection will go on to further deterioration of hearing loss.

The correlation of CMV IgG avidity test for all 60 cases with SNHL disease, showed a weak positive correlation value with 0.138 as more predictive and acceptable test for screening and diagnosis of child with CMV infection and the degree of SNHL disease, while the correlation of rtPCR test for all 60 cases with SNHL disease found a weak negative correlation with -0.246, as the rtPCR is not predictive test for screening of CMV infection and degree of SNHL disease because the shedding of the virus in body fluid may be absent in latent stage of infection and not associated with anti-CMV-IgG low avidity index .

Similar to the findings from studies conducted in populations with different CMV seroprevalence rates in the U.S. and Europe [13,19,20] the results of our study indicated that symptomatic infants were significantly more likely to develop SNHL than those with asymptomatic infection [19,20]. Thus, the presence of CMV-related symptoms at birth is a strong predictor of hearing loss, even in populations with high maternal CMV seroprevalence rate. Our findings demonstrate that congenital CMV infection is an important cause of hearing loss, including bilateral and severe to profound deficit, even with maternal seroimmunity is nearly universal. CMV IgG avidity is an effective tool for assessing risk of transmission. The followed pregnancy outcomes to identify cases of congenital CMV infection; found a strong association between low CMV IgG avidity during pregnancy and increased risk of in utero transmission [21-24]. One study reported that 89% of transmitting women exhibited low IgG avidity [24] in another report [22] however; they found that only 50% (7/14) of transmitting women had low IgG avidity. Evaluating the result from this study showed only few patients with low avidity and the majority with high CMV-IgG avidity that may protect from virus transmission. Patients with high CMV IgG avidity during the first trimester can be assured that the risk of giving birth to an infected infant is low, and invasive procedures to identify fetal infection (e.g., collection of amniotic fluid for viral culture and CMV DNA detection [25] are not needed. Women with low avidity, regardless of trimester, should be considered candidates for further testing to assess fetal infection status [26,27].

Conclusion

CMV IgG avidity testing is now a proven, valuable laboratory tool for diagnosing primary CMV infection during pregnancy. Low avidity indicates primary infection within the preceding 3 to 4 months, with an increased risk of intrauterine transmission to the fetus/newborn. High avidity during the first trimester excludes post conception primary infection and indicates a low risk of intrauterine transmission. CMV IgG avidity and CMV IgM avidity testing performed on CMV IgG-positive samples. Manufacturers are encouraged to seek solutions to distribution and regulatory issues that currently block the widespread availability of their products, thus enabling the global application of CMV IgG avidity testing as a tool for assessing CMV transmission risk during pregnancy.

References

1. Pinhata MMM, Yamamoto AY, Brito RMM, et al. Birth prevalence and natural history of congenital cytomegalovirus infection in a highly seroimmune population. Clin Infect Dis 2009; 49(4): 522-28.

2. Kenneson A, Cannon MJ. Review and meta-analysis of the epidemiology of congenital cytomegalovirus (CMV) infection. Rev Med Virol 2007; 17(4): 253-76.
3. Hamilton ST, van Zuylen W, Shand A, et al. Prevention of congenital cytomegalovirus complications by maternal and neonatal treatments: a systematic review. Rev Med Virol 2014; 24(6): 420-33.
4. http://www.wales.nhs.uk/sitesplus/documents/980/EarlyAssessmentGuidance2013Wales%28i%29.pdf
5. Manicklal S, Emery VC, Lazzarotto T, et al. The "silent" global burden of congenital cytomegalovirus. Clin Microbiol Rev 2013; 26(1): 86-102.
6. Pellegrinelli L, Alberti L, Pariani E, et al. Diagnosing congenital cytomegalovirus infection: don't get rid of dried blood spots. BMC Infectious Diseases 2020; 20(1).
7. Dollard SC, Grosse SD, Ross DS. New estimates of the prevalence of neurological and sensory sequelae and mortality associated with congenital cytomegalovirus infection. Rev Med Virol 2007; 17(5): 355-63.
8. Dahle AJ, Fowler KB, Wright JD, et al. Longitudinal investigation of hearing disorders in children with congenital cytomegalovirus. J Am Acad Audiol 2000; 11(5): 283-90.
9. Yoshinaga-Itano C. Early intervention after universal neonatal hearing screening: impact on outcomes. Ment Retard Dev Disabil Res Rev 2003; 9(4): 252-66.
10. Moretta LR, Biassoni C, Bottino C, et al. Human NK cells and their receptors. Microbes Infect 2002; 4(15): 1539-1544.
11. Vauloup-Fellous C, Berth M, Heskia F, et al. Re-evaluation of the VIDAS® cytomegalovirus (CMV) IgG avidity assay: determination of new cut-off values based on the study of kinetics of CMV-IgG maturation. J Clin Virol 2013; 56(2): 118-123.
12. Attard-Montalto SP, English MC, Stimmler L, et al. Ganciclovir treatment of congenital cytomegalovirus infection: a report of two cases. Scand J Infect Dis 1993; 25(3): 385-8.
13. Maidji E, McDonagh S, Genbacev O, et al. Maternal antibodies enhance or prevent cytomegalovirus infection in the placenta by neonatal Fc receptor-mediated transcytosis. Am J Pathol 2006; 168(4): 1210-26.
14. McCrary H, Sheng X, Greene T, et al. Longterm hearing outcomes of children with symptomatic congenital CMV treated with valganciclovir. Int J Pediatr Otorhinolaryngol 2019; 118: 124-127.
15. Boppana SB, Ross SA, Novak Z, et al. Dried blood spot real-time polymerase chain reaction assays to screen newborns for congenital cytomegalovirus infection. JAMA 2010; 303(14): 1375-1382
16. Foulon I, Naessens A, Foulon W, et al. A 10 year prospective study of sensorineural hearing loss in children with congenital cytomegalovirus infection. J Pediatr 2008; 153(1): 84-8.
17. Yamamoto AY, Mussi-Pinhata MM, Isaac M de L, et al. Congenital cytomegalovirus infection as a cause of sensorineural hearing loss in a highly immune population. Pediatr Infect Dis J 2011; 30(12): 1043-6
18. American Academy of Pediatrics, Joint Committee on Infant Hearing. Year 2007 position statement: Principles and guidelines for early hearing detection and intervention programs. Pediatrics 2007; 120(4): 898-921.
19. Ahlfors K, Ivarsson SA, Harris S, et al. Congenital cytomegalovirus infection and disease in Sweden and the relative importance of primary and secondary maternal infections. Preliminary findings from a prospective study. Scand J Infect Dis. 1984; 16(2): 129-137.
20. Navti OB, Al-Belushi M, Konje JC, et al. Cytomegalovirus infection in pregnancy - an update. Eur J Obstet Gynecol Reprod Bio 2021; 258: 216-222.
21. Grangeot-Keros L, Mayaux MJ, Lebon P, et al. Value of cytomegalovirus (CMV) IgG avidity index for the diagnosis of primary CMV infection in pregnant women. J Infect Dis 1997; 175(4): 944-996.
22. Bodeus M, Van Ranst M, Bernard P, et al. Anticytomegalovirus IgG avidity in pregnancy: a 2-year prospective study. Fetal Diagn Ther 2002; 17(6): 362-366.
23. Lazzarotto T, Spezzacatena P, Varani S, et al. Anti-Cytomegalovirus (anti-CMV) immunoglobulin G avidity in identification of pregnant women at risk of transmitting congenital CMV infection Clin Diagn Lab Immunol 1999; 6(1): 127-129.
24. Lazzarotto T, Varani S, Spezzacatena P, et al. Maternal IgG avidity and IgM detected by blot as diagnostic tools to identify pregnant women at risk of transmitting cytomegalovirus. Viral Immunol 2000; 13(1): 137-41.
25. Lazzarotto T, Varani S, Gabrielli L, et al. New advances in the diagnosis of congenital cytomegalovirus infection. Intervirology 1999; 42: 390-397.
26. Lazzarotto T, Varani S, Guerra B, et al. Prenatal indicators of congenital cytomegalovirus infection. J Pediatr 2000; 137(1): 90-95.
27. Bodeus M, Goubau P. Predictive value of maternal-IgG avidity for congenital human cytomegalovirus infection. J Clin Virol 1999; 12(1): 3-8.

*Correspondence to:

Ahmed Hameed Hasan

Department of Microbiology

Basrah Medical College

Baghdad

Iraq

Tel: +964 771-291-3336

E-mail: drnihadkhalawe@gmail.com