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Predisposing factors to cytomegalovirus infection among pregnant women in North-Western Nigeria.Gadama, A.S.^{1*}, Sarkinfada, F.², Mohammed, Y.³, Basirka, N.L.⁴, Abubakar, M.U.⁵

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Author for Correspondence*: abdullahigadama@yahoo.com/ +234-803-796-9591**Abstract**

Cytomegalovirus infection is the most common intrauterine infection prevalent worldwide but more in communities with poor socioeconomic status and low level of sanitation. It is usually beneath the threshold of clinical recognition but could cause serious illness in the developing foetus and immunocompromised. Low socioeconomic status, increasing parity, older age and immunocompromised state are known to favor the virus transmission. The aim of the study was to identify risk factors for CMV seropositivity to guide on possible prevention and control. The study was a cross-sectional descriptive study, combining the use of a structured questionnaire and analysis of serum samples obtained from 174 apparently healthy pregnant women attending ANC at General Hospital Jahun, Jigawa State- Nigeria. The serum samples were analyzed for IgG and IgM antibodies to CMV by Enzyme-linked immunosorbent assay (ELISA). Of the 174 apparently healthy pregnant women, 152 (87.4%) were seropositive for at least Immunoglobulin M or Immunoglobulin G against CMV. There was a statistical significant association between CMV-Specific IgG seropositivity and marriage setting ($p=0.018$) with majority of clients being in polygamous setting. However, no significant association was demonstrated statistically with other factors (p -value <0.05). With marriage setting identified as risk factor for CMV seropositivity, many children are at risk of congenital cytomegalovirus infection and its manifestations especially those that are product of polygamous setting. Therefore, there is need for an intervention policy for the prevention and control of

cytomegalovirus infection in the study area.

Keywords: *Cytomegalovirus, Risk factors, pregnant women, Nigeria*

Introduction

Human cytomegalovirus (CMV) is a highly host specific member of the Human Herpesviridae family. Herpesviridae family members include Herpes Simplex virus (HSV) type 1 and 2, Varicella Zoster virus (VZV) and Epstein-Barr virus (EBV). Cytomegalovirus is ubiquitous and the largest virus in the family and is morphologically indistinguishable from other human herpesviruses (Sinzger *et al.*, 1995).

Infection with CMV could take either primary or non-primary forms. Cytomegalovirus infection in a previously seronegative person is termed primary form of infection. Reactivation can occur in previously infected person following virus dormancy usually in conditions of immunosuppression. With the knowledge of the emergence of several strains of CMV through molecular studies, reinfection can therefore occur even in immunocompetent individuals when previously infected person is re-infected by a virus distinct from the initial one (Yinon *et al.*, 2010). Cytomegalovirus recurrent infection, reinfection and reactivation of primary infection are termed non-primary CMV infection. Reinfection and reactivation constitute a sub-set of non-primary infection termed secondary CMV infection (Revello *et al.*, 2011). Reactivation and re-infection forms of infection give rise to recurrent infection (Alford *et al.*, 1990; Yinon *et al.*, 2010).

Cytomegalovirus is usually an asymptomatic infection in immunocompetent individuals, symptomatic disease usually non-specific and manifest as infectious mononucleosis characterized by malaise, headache, sore throat and fatigue. Fever is also commonly present and may persist for weeks in 98% of cases of cytomegalovirus mononucleosis. Lymphadenopathy, pharyngitis and splenomegaly are each seen in 30% of CMV patients (Pass, 2001; Yeroh *et al.*, 2015). Seroconversion occurs in 1% to 4% of all pregnancies and is higher in women who are of low socioeconomic status or who have poor personal hygiene (Yinon *et al.*, 2010; Hagay *et al.*, 1996; Hanshaw, 1995).

Other clinical abnormalities of CMV infection in normal host include Guillain-Barre, retinitis, thrombocytopenia, gastrointestinal ulceration, hepatitis and pneumonia (Schleiss, 2010). In HIV/AIDS patient, the symptoms are often severe and may include retinitis, enterocolitis, esophagitis, gastritis, immune recovery vitritis - posterior segment inflammation and pneumonitis (Schleiss, 2010).

Cytomegalovirus is the most common viral etiology of mental retardation and auditory disorder of children in developed countries (Rahav *et al.*, 2007). Sensorineural hearing loss (SNHL), seizures, chorioretinitis, mental retardation, speech and psychomotor delays, learning disabilities and dentition disorders are the most frequent long-term consequences of Congenital CMV infection (Fowler and Boppana, 2006). In few cases, there are symptoms at birth which include premature delivery, small for gestational age, jaundice, rashes and feeding difficulties (Yeroh *et al.*, 2015; Colungnati *et al.*, 2007).

Several studies in the developed world have demonstrated a strong association between primary CMV infection of the mother and vertical CMV transmission. The risk of congenital infection is approximately 40% in babies born to mothers who acquire a primary CMV infection after conception. In contrast, the risk is only about 1% in infants born to mothers with non-primary CMV infection (Dollard *et al.*,

2014). Since the main burden of congenital infections in developed nations results from primary infections, therefore, non-primary infections may represent the main cause of CMV vertical transmission in developing countries since higher seroprevalence was noticed in the regions (Saldan *et al.*, 2017; Mussi-Pinhata *et al.*, 2009).

During the course of an infection, the host excretes viral particles in urine, blood, semen and saliva. Therefore, people can be easily infected (including pregnant women) by person to person contact, sexual contact or taking care of young infected children (Syggelou *et al.*, 2010). Vertical transmission of CMV from mother to fetus may occur during pregnancy, thus excluding virus transmission from mother to newborn infant (Hyde, 2014; Hyde *et al.*, 2014; Kenneson and Cannon, 2007; Pass *et al.*, 2006).

Presently, the gold standard for determining primary infections is CMV seroconversion, which is the detection of CMV IgG in a previously non-immune pregnant woman. Since pre-conception serologic screening for CMV is not routinely performed in most countries including Nigeria, seroconversion data may often not be available. As such the detections of CMV IgM and low-avidity IgG remains the only option for primary CMV infection detection as it has been proven to be effective (Saldan *et al.*, 2017; Daiminger *et al.*, 2005).

Cytomegalovirus infection has worldwide endemic distribution with no seasonal variation (Revello *et al.*, 2011). Although CMV is widely distributed, CMV epidemiology is diverse as its transmission is deeply related to low sanitarian conditions and high population density. The Prevalence of CMV is dependent on multiple factors, including socioeconomic status, age, parity, occupation and immune status (Betts, 1983). Seropositivity correlates with increasing parity, lower socio-economic level, older age, number of sex partners and immune system status such as HIV etc. (Chandle *et al.*, 1985).

Serological surveys have shown CMV infections virtually present in every population that have been tested (Okwori *et al.*, 2008), with

seroprevalence among women in the reproductive age ranges from 45% in developed countries to 100% in developing countries (Plosa *et al.*, 2012).

In Northern Nigeria, the prevalence is as high as 98.7% in Sokoto (Ahmad *et al.*, 2011), 79.1% in Maiduguri (Babayo *et al.*, 2014) and 94.8% in Kaduna (Yeroh *et al.*, 2015).

The treatment of congenital infections is complex and controversial. Available antiviral drugs, such as ganciclovir, cidofovir and foscarnet, are commonly used in immunocompromised patients, but their toxicity (especially renal and haematological) and teratogenic effects restrict their use during pregnancy (Benoist *et al.*, 2013).

A pilot study performed in France assessed the pharmacological efficacy of oral valacyclovir in cases of congenital infection. The drug was able to reach therapeutic levels in both maternal and foetal blood and also had effect on the viral load in fetal blood (Naddeo *et al.*, 2015; Jacquemard *et al.*, 2007). The aim of the study was not to evaluate therapeutic effects, but however, its results are encouraging.

Another study was conducted in Italy to analyze the efficacy of a treatment with CMV hyper-immune globulin for maternal primary CMV infection. Promising results for prevention and treatment of congenital infection with no signs of side effects was observed (Benoist *et al.*, 2013). The study has also shown that hyper-immune globulin has immunomodulatory effects that can decrease the pathogenic effects of CMV (Naddeo *et al.*, 2015; Nigro *et al.*, 2015).

The ultimate goal in prevention of congenital CMV infection is to develop a vaccine, which would be administered to seronegative women of childbearing age to prevent the occurrence of primary CMV infection during pregnancy (Yinon *et al.*, 2010).

Despite the high prevalence of CMV in Nigeria, no policy on the prevention and control of CMV infection. Thus, CMV infections is said to be neglected health problem in Nigeria. Several

European countries (Austria, Belgium, France, Germany, Italy, Netherland, Portugal, and Spain) offer serologic CMV screening and counseling to pregnant women (Saldan, *et al.*, 2017; Adler, 2011). CMV testing is also recommended for pregnant women only when there is clinical suspicion of CMV infection, or when foetal abnormalities are detected by routine imaging in USA (Saldan *et al.*, 2017; CDC, 2008). Therefore, a research of this kind is timely as it would highlight the possible risk factors for CMV transmission and recommend to the policy makers the need for an intervention measure for the prevention and control of this endemic disease. But until a vaccine is available, improvising personal and environmental hygiene remains the practical option.

Materials and Methods

Study Area

The study was carried out in General Hospital Jahun. Jahun Local Government is located in Jigawa state North-Western Nigeria at 12° 04' N, 9° 38' E with a land mass of 1,172km² and a population of 229,094 according to 2006 census. General Hospital Jahun is the only secondary health facility in the local government and serve as a referral center to most neighboring towns.

Study Population

The study included all consenting pregnant women attending antenatal clinic in General Hospital Jahun of Jigawa state between January and March 2017.

Sample Collection

Five milliliters of whole blood sample were collected from consented clients aseptically using vacutainer needles. A semi-structured researcher administered questionnaire was used to obtain Socio-demographic profile of clients.

Ethical Consideration

Ethical clearance was obtained from the Jigawa State Ministry of Health. The study was explained to the patients and verbal informed consent was obtained before sample collection and administration of questionnaire for Socio-demographic data collection.

Sample Analysis

Blood samples were analyzed for IgG and IgM detection using Enzyme-linked immunosorbent assay (ELISA) following manufacturers guide. (Foresight[®], ACON Laboratories, Inc. 10125 Mesa Rim Road, San Diego, CA 92121, USA).

Statistical Analysis

Data obtained were analyzed using Microsoft and SPSS software version 20 (2011, IBM Corp.). Sociodemographic data/identified risk factor were summarized inform of tables and presented in percentages. Chi square test was used to test for association between Socio-demographic data/ Identified risk factors and CMV-specific IgM/IgG antibodies with a p-value of ≤ 0.05 considered significant.

Results

One hundred and seventy-four pregnant women were screened for antibodies against CMV. Table 1 shows their sociodemographic characteristics.

The mean age was 25.4 ± 5.1 years, with a range of 15 to 45 years. Ninety-three (53.4 %) were between 15-24 years of age, while only 22 (12.6%) belongs to the 35 years and above category. Fifty-nine (33.9%) belongs to 25-34 years category. More than half of the clients were in second trimester of pregnancy (54.6%), sixty-seven (38.5) were in the third trimester, while only few (6.9%) belongs to the first trimester of pregnancy category. Most of the clients were multiparous (61.5%), thirty (20.7%) of them were pregnant for the first time while thirty-one (17.8) were in their second pregnancy. Ninety-two of them live in polygamous setting while eighty-two live in a monogamous setting. The Overall seroprevalence is 87.4% consisting all pregnant women that are positive to at least IgM or IgG Specific antibody. There was a statistical significant association between marriage setting and IgG seropositivity alone (Tables 2 and 3). However, no significant association between IgM and IgG with remaining Socio-demographic factors tested.

Table 4.1. Sociodemographic characteristics of pregnant women (n=147).

Characteristics	Number	Percentage
Age Group		
15-24	93	53.4
25-34	59	33.9
Above 35	22	12.6
Gestational age		
1 st trimester	12	6.9
2 nd trimester	93	54.6
3 rd trimester	67	38.5
Parity		
Nullipara	36	20.7
Primipara	31	17.8
Multipara	107	61.5
History of Miscarriage		
None	125	71.8
Once	43	24.7
Atleast twice	6	3.4
Marriage setting		
Monogamy	82	47.1
Polygamy	92	52.9

Table 2: Comparison of the CMV-specific IgM by Sociodemographic factors (n=174)

Characteristics	CMV-Specific IgM			p-value
	Positives	Negatives	Total	
Age Group				
15-24	29(31.1)	64(68.8)	93(53.5)	2.154
25-34	12(20.3)	47(79.7)	59(33.9)	
Above 35	6(27.3)	16(72.7)	22(12.6)	
Gestational age				
1 st trimester	1(8.3)	11(91.7)	12(6.9)	3.424
2 nd trimester	24(25.3)	71(74.7)	95(54.6)	
3 rd trimester	22(32.8)	45(67.2)	67(38.5)	
Parity				
Nullipara	11(30.6)	25(69.4)	36(20.7)	1.208
Primipara	6(19.4)	25(80.6)	31(17.8)	
Multipara	30(28.0)	77(72.0)	107(61.5)	
Marriage setting				
Monogamy	23(28.0)	59(72.0)	82(47.1)	0.085
Polygamy	24(26.1)	68(73.9)	92(52.9)	

Table 3: Comparison of the CMV-specific IgG by Sociodemographic factors (n=174)

Characteristics	CMV-Specific IgG			P-value
	Positives	Negatives	Total	
Age Group				
15-24	81(87.1)	12(12.9)	93(53.5)	2.208
25-34	46(78.0)	13(22.0)	59(33.9)	
Above 35	18(81.8)	4(18.2)	22(12.6)	
Gestational age				
1 st trimester	9(75.0)	3(25.0)	12(6.9)	1.208
2 nd trimester	78(82.1)	17(17.9)	95(54.6)	
3 rd trimester	58(86.6)	9(13.4)	67(38.5)	
Parity				
Nullipara	30(83.3)	6(16.7)	36(20.7)	1.007
Primipara	24(77.4)	7(22.6)	31(17.8)	
Multipara	91(85.0)	16(15.0)	107(61.5)	
Marriage setting				
Monogamy	68(82.9)	14(17.1)	82(47.1)	0.018
Polygamy	77(83.7)	15(16.3)	92(52.9)	

Discussion

Cytomegalovirus is one of the most successful human parasites. Conveniently, CMV survives in its human host in latent form and could be reactivated under favoring circumstances. It is transmitted both vertically from mother to foetus and horizontally from one person to another.

The overall seroprevalence of CMV infection among pregnant women in this study was 87.4%. The only significant association obtained in this study was between CMV-specific IgG and marriage setting with majority of the clients in polygamous setting. Although IgM is the only measure of primary infection in this study due to

the limitation from lack of preconception serological evidence of IgG. CMV-specific IgG still remains relevant as it may denote seroconversion which is currently the Gold standard for CMV primary infection detection (Saldan *et al.*, 2017; Daiminger *et al.*, 2005). Therefore, more efforts are needed in premarital, preconception and antenatal screening and treatment in order to reduce the rising prevalence of CMV in Northern Nigeria.

This finding agreed with the results of Bate *et al.* (2010) in the United States which demonstrated association with age and not with other factors (Khairi *et al.*, 2013) in Sudan that demonstrated

association between antibodies and age, history of abortion only but not with other factors and Deborah *et al.* (2015) in Nigeria that demonstrated relationship between CMV-Specific IgM antibodies with age but not with other factors. The fact that there were no association related to the age of the women in this study, indicates exhibition of similar behavior of the correspondents across all category of ages. The result is however in conformity with that obtained in Iran (Delfan-Beiranvand *et al.*, 2011) and in Yemen (Alghalibi *et al.*, 2016).

Considering the social and cultural practices of the populace in the study area, the issue of polygamy in transmission of infectious diseases could be significant. In this study marriage setting was found to be significantly associated with presence of IgG antibodies ($p=0.018$). This could be viewed in terms of multiple sexual partners favors the transmission of CMV infection.

Northern Nigeria is leading in terms of polygamy practices in Nigeria (Verma and Sangha, 1982). Polygamy practice may not be the fault but rather the poor infection control measures surrounding the practice. Policy on pre-marital screening exists in some Nigerian States, but it is restricted to sickle cell, hepatitis (Hepatitis B and C) and retroviral infection (HIV). Cytomegalovirus screening is not offered pre-maritally even in the HIV/AIDS population at risk of symptomatic infection. Therefore, an intervention policy if constituted would help reduce the prevalence of cytomegalovirus among pregnant women in Nigeria and thus, reduce the risk of congenital CMV and its sequelae in children.

Conclusion

With the identified risk factor as polygamy practice, premarital screening and treatment would go a long way in reducing the prevalence of CMV in the study area and hence, preventing congenital CMV among neonates and symptomatic infection in the immunocompromised.

Recommendation

1. There is need to develop policy for screening and treatment of the seropositive population before marriage especially in the immunosuppressed individuals and preconception/antenatal screening and management for the entire population.
2. There is need to develop a vaccine, which would be administered to seronegative women of childbearing age to prevent the occurrence of primary CMV infection during pregnancy. Until an effective vaccine is available, seronegative pregnant women should practice good personal hygiene such as avoiding intimate contact with salivary secretions and urine from infected persons, careful hand washing after changing diapers of babies and wiping secretions
3. There is need to launch a nationwide campaign on CMV infection awareness and control strategies in Nigeria.

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