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The Impact of Maternal HIV and Malaria Infection on the Prevalence of Congenital Cytomegalovirus Infection in Western Kenya

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Abstract

Background: Data on congenital cytomegalovirus (CMV) infection in Africa are limited.

Objective: To describe the prevalence of congenital CMV infection in a population with high prevalence of maternal HIV and malaria infection in western Kenya.

Study design: We screened newborns for CMV by polymerase chain reaction assay of saliva swabs and dried blood spots (DBS), and assessed maternal CMV immunoglobulin G (IgG) status by testing serum eluted from newborn's DBS. We calculated adjusted prevalence ratios (aPRs) using log-binomial regression models.

Results: Among 1066 mothers, 210 (19·7%) had HIV infection and 207 (19·4%) had malaria infection; 33 (3.1%) mothers had both. Maternal CMV IgG prevalence was 93·1% (95% confidence interval [CI]: 88·3%–96·0%). Among 1078 newborns (12 sets of twins), 39 (3·6%, 95% CI: 2·7–4·9%) were CMV positive. The prevalence of congenital CMV infection by maternal HIV and malaria infection status was 5·0% (95% CI: 2·7–9·2%) for HIV only, 5·1% (95% CI: 2·7–9·4%) for malaria only, 8·8 (95% CI: 3·1–23·0) for HIV and malaria co-infection, and 2·6% (95% CI: 1·7–4·1%) for none. Congenital CMV infection was independently associated with maternal HIV infection (aPR=2·1; 95% CI: 1·0–4·2), adjusting for maternal age, parity, and malaria infection.

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Conflicts of interest

The authors have no conflicts of interest to disclose.

Conclusions: The prevalence of congenital CMV infection was higher than the 0·2–0·7% in developed countries. Maternal HIV infection may increase the risk of congenital CMV infection, but the role of maternal malaria on intrauterine transmission of CMV remains unclear.

Keywords

cytomegalovirus; malaria; HIV infections; prevalence; Kenya

Background

Congenital cytomegalovirus (CMV) infection may result in foetal or infant death, severe disease with central nervous system involvement, transient manifestations during the neonatal period (e.g., mild hepatomegaly), isolated sensorineural hearing loss (SNHL), or asymptomatic infection with no long-term sequelae.[1,2] About 10% of infected infants have symptomatic disease at birth, which is associated with higher risk of neurodevelopment impairment. However, among the 90% of infected infants who are asymptomatic at birth, 10% may develop SNHL.[3]

The overall prevalence of congenital CMV infection ranges from 0·2–0·7% in developed countries[3,4] to 0·6–6·1% in developing countries.[5] There are limited data on the prevalence of congenital CMV infection in Africa. In two population-based studies, the prevalence of congenital CMV infection was 1·4% in Ivory Coast[6] and 5·4% in The Gambia.[7] In studies conducted among infants born to HIV-infected mothers in Africa, the prevalence of congenital CMV infection ranged from 2·3% to 11·4% in HIV-exposed uninfected infants[8–14], to 10·0% to 28·6% in HIV-infected infants.[8,12] The higher prevalence of congenital CMV infection in those studies suggest a possible association of maternal HIV infection and intrauterine transmission of CMV. Nonetheless, most of the studies were limited by their small sample size and did not include HIV-unexposed infants for comparison.

Malaria infection in pregnancy has also been postulated to increase intrauterine transmission of CMV. A study conducted in The Gambia during 2002–2005 found a 2-fold higher prevalence of congenital CMV infection among infants born to mothers who had placental malaria parasitaemia.[7] However, that study did not assess maternal HIV status, which could have confounded the association of malaria and congenital CMV infection, since the prevalence of HIV infection in The Gambia in the early 2000s was high (17·5%).[15]

Objectives

To describe the prevalence of congenital CMV infection and factors associated with intrauterine transmission of CMV in Western Kenya, an area known for its high prevalence of HIV and malaria infections.

Study design

The study was conducted in two public facilities in Siaya County, western Kenya: the Siaya County Referral Hospital and the Bondo sub-County Hospital. Infants born from November

2015 to October 2017 whose mothers were participating in a prospective cohort study to measure the impact of influenza on birth outcomes were eligible to participate in our CMV substudy. We approached mothers during their first post-natal visit to obtain informed consent for collection of newborns' blood and saliva for CMV testing. We collected dried blood spots (DBS) through a heel prick that was spotted onto filter paper. Collection of saliva swabs occurred 1 hour or more after the newborn was breastfed and stored dry in specimen tubes. Study personnel transported specimens to the laboratory within 8 hours after collection and stored under refrigeration or −20°C until shipped to CDC for testing. We used polymerase chain reaction (PCR) assay to assess newborn CMV status, using DNA eluted from both DBS and saliva specimens using Extracta (Quantabio, Beverly, Massachusetts). We categorized a newborn as having congenital CMV infection if either saliva or DBS were positive for CMV by PCR targeting the viral immediate early region.[16] We assessed maternal CMV immunoglobulin G (IgG) status using serum eluted from a random sample of the DBSs tested by immunofluorescence assay (Bion International).

Study nurses collected maternal and newborn demographic and clinical data during the interview with the mother and by reviewing medical records. Maternal data included age, number of previous pregnancies and live births, marital status, education level, trimester of pregnancy at enrolment in the influenza study, HIV status, highly active antiretroviral therapy (HAART) status and duration for HIV-infected mothers, and malaria infection. The mothers received intermittent preventive malaria treatment during pregnancy, and those diagnosed with malaria infection by rapid diagnostic test, which was performed at enrolment and throughout pregnancy in the event of a sick visit with fever, were offered treatment.

As part of the influenza study, all newborns were examined at birth and followed with weekly visits up to 12 weeks of life. Study nurses contacted mothers of CMV-positive infants once results were available (after the 12-week follow-up visit) to arrange for a paediatric review appointment. A paediatrician evaluated the CMV-positive infants at 4 and 24 months of age. The paediatrician explained to the mothers/parents the relevance of a positive CMV result at birth; collected a detailed infant developmental history including motor, fine motor, speech and social/cognitive development; and performed physical and age-appropriate neurological examinations, and hearing and vision screenings. The Centers for Disease Control and Prevention's Institute Review Board relied on the scientific and ethical review unit at the Kenya Medical Research Institute (KEMRI) for review and approval the study protocol (SSC-2981).

We defined preterm birth as delivery before 37 weeks and 0 days gestational age (GA), assessed by Ballard exam and small for GA as birth weight $<10^{th}$ percentile for GA using the Landis foetal weight nomogram from the Democratic Republic of the Congo.[17] We estimated that a sample size of approximately 1000 newborns would allow us to detect a difference of 3% or greater in the prevalence of congenital CMV infection among those born to HIV-infected mothers compared to HIV-uninfected mothers, with a power of 80% and alpha=0·05, using a 1-sided Pearson's Chi-squared test. Our sample size calculation was based on two assumptions: 25% maternal HIV prevalence[18], and 1% prevalence of congenital CMV infection among infants born to HIV-uninfected mothers.[5]

We estimated the prevalence of congenital CMV infection and 95% confidence intervals (CI) by maternal and newborn characteristics. We used Chi-square or Fisher exact tests to compare categorical variables and student *t* or ANOVA tests for continuous variables. To evaluate the association of maternal characteristics with congenital CMV infection, we calculated univariate prevalence ratios (PRs) and 95% CI using the exact method. To calculate adjusted PRs (aPRs) for maternal age group, parity, HIV and malaria infection, we used log-binomial regression models. Because twins share maternal risk factors, we repeated the models excluding the second-born twins. We considered results with p< 0·05 as statistically significant. We carried out data analysis using SAS version 9·4 (SAS Institute, Cary, NC, USA) software package.

Results

Of the 1079 mothers approached, 1066 consented to participate in the CMV substudy, among whom 51·8% were <25 years of age, 73·9% were multipara, 86·1% were married, 59·6% had primary school education or less, and 69·5% were enrolled in the influenza cohort during their second trimester of pregnancy (Table 1). Maternal CMV IgG prevalence was 93·1% (95% CI: 88·3–96·0%; n/N=162/174 among randomly selected samples). Two-hundred-ten (19·7%) mothers had HIV infection: 206 had HIV infection at enrolment and four at delivery. Only 238 (27·7%) of the 860 HIV-uninfected mothers were tested for HIV at delivery. Malaria infection was diagnosed at enrolment or during follow-up in 207 (19·4%). Thirty-three (3·1%) mothers had both HIV and malaria infection, and 682 (64·0%) had neither HIV nor malaria infection diagnosed during pregnancy (Table 1).

We collected specimens for CMV testing of 1078 newborns (including 12 twin pairs) within a median of 3 days after birth (interquartile range: 2–5 days). Thirty-nine (3·6%, 95% CI 2·7%–4·9%) newborns were CMV positive, including 36 (92·3%) singletons and three (7·7%) twins (one concordant twin pair and one discordant twin). The CMV-positive twin pair was born to an HIV-infected mother and the discordant twin, to a mother without HIV or malaria infection. There were no significant differences among CMV-positive and CMV-negative newborns (Table 2). None of the 39 CMV-positive newborns had abnormal clinical signs, such as petechiae/purpura, splenomegaly, hepatomegaly, jaundice, or microcephaly at birth. Twenty-three (2·2%) CMV-negative newborns presented with at least one abnormal clinical sign (Table 2). Eight of the 39 CMV-positive infants have reached 24 months of age and completed the neurodevelopmental follow-up by the time of this analysis; one was diagnosed with a speech delay. Follow-up is ongoing.

In univariate analysis, maternal demographics, HIV infection, and malaria infection were not significantly associated with congenital CMV infection (Table 3). The median duration of HAART among HIV-infected mothers who had a CMV-positive newborn was 633 days (range: 321–1701; n=11) vs. 864 days (range: 258–2154; n=192) for those who had a CMV-negative newborn (p=0·746). All seven HIV-infected mothers not receiving HAART had CMV-negative newborns. The prevalence of congenital CMV infection by maternal HIV and malaria infection status was 5·0% (95% CI: 2·7–9·2%) for HIV only, 5·1% (95% CI: 2·7–9·4%) for malaria only, 8·8 (95% CI: 3·1–23·0) for HIV and malaria co-infection, and 2·6% (95% CI: 1·7–4·1%) for none (Table 2). .

Our multivariable analysis included maternal age and parity because these variables were associated with both maternal HIV and malaria infection. A higher proportion of HIV-infected vs. HIV-uninfected mothers were ≥25 years (74·3% vs. 41·8%) and multipara (92·4% vs. 69·4%) ($p<0·001$ for both comparisons). A higher proportion of mothers with vs. without malaria infection were <25 years (62·8% vs. 49·1%) and primipara (40·6% vs. 22·6%) ($p<0·001$ for both comparisons). Maternal HIV infection (aPR=2·1; 95% CI: 1·0–4·2; $p=0·043$) but not malaria infection (aPR=1·7; 95% CI: 0·9–3·4; $p=0·107$) was independently associated with congenital CMV infection, after adjusting for maternal age and parity (Table 4). Excluding the second-born twins, the point estimates remained similar but neither maternal HIV infection (aPR=2·0; 95% CI: 1·0–4·3; $p=0·056$) nor malaria infection (aPR=1·9; 95% CI: 1·0–3·7; $p=0·067$) were significantly associated with congenital CMV infection (Table 4).

Discussion

Our study assessed the prevalence of congenital CMV infection in a population with high prevalence of HIV and malaria in western Kenya. We found high maternal CMV seroprevalence (93·1%), and a prevalence of 2.6% of congenital CMV infection among infants born to HIV- and malaria-uninfected mothers. Maternal HIV infection seemed to be associated with increased risk of congenital CMV infection, after controlling for maternal age, parity and malaria during pregnancy.

In our study, the crude prevalence of congenital CMV infection among infants born to HIV-infected mothers was 5·6%, about twice as high as for infants born to HIV-uninfected mothers, though not statistically significant. In several studies among infants born to HIV-infected mothers in Africa, the prevalence of congenital CMV infection ranged from 2·3% to 11·4%.[8–14] The wide prevalence range may be due to differences in sample size, laboratory methods and specimens used for CMV testing (urine, saliva, cord blood, or sera), and population tested (general infant population vs neonatal unit patients), but may also reflect true differences by population. Although the prevalence of congenital CMV infection was generally higher in studies among infants born to HIV-infected mothers, most studies have not included HIV-unexposed infants for comparison, which would be important for understanding the impact of HIV infection on the prevalence of congenital CMV infection.

The impact of HAART on intrauterine transmission of CMV infection has not been evaluated in populations with high prevalence of maternal HIV infection in Africa. In a study of >4500 infants born to HIV-infected mothers in France, maternal use of HAART increased from 9·6% in 1997 to 73·3% in 2004 and the prevalence of congenital CMV infection decreased from 3·2% to 1·2% after HAART introduction.[19] However, despite the significant time trend observed in France, the type of antiretroviral therapy (HAART, mono, dual-drug, or no therapy) was not significantly associated with congenital CMV infection.[19] Similarly, studies from South Africa have not found significant differences in the prevalence of congenital CMV infection in subsets of infants born to HIV-infected mothers receiving HAART vs. prenatal zidovudine (3·1% vs. 2·7%)[10], or among infants born to mothers not receiving HAART because HIV infection was diagnosed at the time of labor (2.2%).[20] It appears that the most important factor associated with congenital CMV infection among

infants born to HIV-infected mothers is maternal CD4 counts less than 200 cells/μl during pregnancy.[10,19,21] Although in our study we did not have data on maternal CD4 count and viral load, most HIV-infected mothers were on HAART. We found no differences in the duration of HAART among mothers who had infants with or without congenital CMV infection.

About 10% of newborns with congenital CMV infection are expected to have symptomatic disease at birth, though mild signs may go unnoticed in the absence of screening.[5] Studies have shown that HIV-infected infants were more likely to have congenital CMV infection and symptomatic disease at birth compared with HIV-exposed uninfected infants.[19,20] In our study, none of the CMV-positive infants had symptomatic congenital CMV disease. We do not think study staff overlooked any evidence of disease since they were trained to look for nonspecific CMV-related signs, which were identified in a small proportion of CMV-negative newborns. Study staff were blind to the newborn's CMV status because specimens were stored for 3–4 months before laboratory testing; therefore, we do not think there was any bias in examination of CMV-positive and CMV-negative infants. However, we were not able to conduct blood tests for measuring bilirubin, platelets, or liver enzyme levels, or newborn hearing or neuroimaging evaluations. Neurodevelopmental follow-up data will be available once all children with congenital CMV infection are 2 years old.

We observed a higher prevalence of congenital CMV infection with maternal malaria infection, albeit not statistically significant. We did not have information on placental malaria parasitaemia, which has been associated with congenital CMV infection in a study from The Gambia.[7] In malaria-endemic areas, placental malaria parasitaemia may occur in the absence of symptoms due to acquired immunity[22], and with low peripheral blood parasite densities, for which current rapid diagnostic tests are less sensitive.[23] Our sample size was relatively small and could not assess whether HIV and malaria co-infection during pregnancy increase the risk of congenital CMV infection. Further evaluation of the potential impact of maternal malaria infection on the burden of congenital CMV infection is warranted.

Our study had several limitations. Pregnant women participating in the influenza cohort study may have had differences in access to HIV and malaria testing and treatment when compared to the general population. Not all mothers who were HIV-negative at enrolment were tested for HIV at delivery. Thus, undiagnosed maternal HIV infections could have hindered our ability to find differences regarding infant's CMV status. Our number of CMV-positive infants was small, and excluding second-born twins from the analysis further reduced the power of the study. We did not collect data on twins' type – limited data from the literature suggest that discordant infection can be expected in dichorionic twins.[24] We did not assess adherence to HAART or level of maternal immunosuppression among HIV-infected mothers. We did not collect additional specimens (i.e., urine) for confirmatory CMV testing. However, most infants had saliva swabs collected within 5 days of birth, when CMV shedding in breastmilk is low, thus the likelihood of CMV contamination from breastmilk was low.

In conclusion, the prevalence of congenital CMV infection among infants born to mothers without HIV or malaria infection was higher than the 0·2–0·7% reported in developed countries. Congenital CMV infection appeared to be associated with maternal HIV infection, despite near universal maternal use of HAART. Further studies are needed to assess the impact of malaria infection on the prevalence of congenital CMV infection. Studies that follow up women enrolled early in pregnancy offer an opportunity to gain a better understanding of epidemiological and immunological factors associated with mother-to-foetus transmission of CMV.

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Table 1.

Maternal demographic and clinical characteristics, Siaya County, Kenya, November 2015–October 2017

Maternal characteristics	n=1066	%
Age		
<25 years	552	51·8
≥25 years	514	48·2
Parity		
Primipara	278	26·1
Multipara	788	73·9
Marital status		
Single	145	13·6
Married *	921	86·4
Education level		
Primary or less	635	59·6
Secondary or higher	431	40·4
Trimester of pregnancy at enrolment		
First	314	29·5
Second	741	69·5
Third	11	1·0
HIV infection at enrolment		
Yes	206	19·3
No	860	80·7
Malaria infection diagnosed at enrolment or follow-up		
Yes	207	19·4
No	859	80·6
HIV and malaria infection at enrolment or follow-up		
Both	33	3·1
HIV infection only **	177	16·6
Malaria infection only	174	16·3
Neither	682	64·0

* Includes five widowed.

** 4 mothers had positive HIV test results at delivery

Table 2.

Clinical characteristics of infants with and without congenital CMV infection, Siaya County, Kenya, November 2015–October 2017

Characteristics	CMV-positive infants n=39 n (%)	CMV-negative infants n=1039 n (%)	p-value
Sex			
Female	22 (56·4)	511 (49·2)	0·375
Male	17 (43·6)	528 (50·8)	
Mode of delivery			
Vaginal	37 (94·9)	990 (95·)	0·707
C-section	2 (5·1)	49 (4·7)	
Gestational age at birth			
<37 weeks	10 (25·6)	168 (16·2)	0·118
≥37 weeks	29 (74·4)	871 (83·8)	
Clinical characteristics at birth			
Small for gestational age *	1 (2·6)	16 (1·5)	0·468
Petechiae	0	11 (1·0)	–
Purpura	0	3 (0·3)	–
Splenomegaly	0	4 (0·4)	–
Hepatomegaly	0	3 (0·3)	–
Jaundice	0	6 (0·6)	–
Seizures	0	5 (0·5)	–
Microcephaly	0	0	–
Neurological abnormalities	0	2 (0·2)	–
Hospital visits during first 6 weeks of life			
No visits	16 (41·0)	354 (34·1)	0·346
1 visit	10 (25·6)	385 (37·1)	
≥2 visits	13 (33·3)	300 (28·9)	

* Six twins were small for gestational age, including one CMV-discordant twin pair, one CMV-negative pair, and two other twins

Table 3.

Prevalence of congenital CMV infection by maternal characteristics, Siaya County, Kenya, November 2015–October 2017

Maternal characteristics	CMV-positive infants n	Infants screened for CMV N	Prevalence (95% CI)	Prevalence Ratio (95% CI)	p-value
Overall	39	1078	3·6 (2·7–4·9)	–	
Age					
<25 years	20	558	3·6 (2·3–5·5)	1·0 (0·5–1·8)	0·951
≥25 years	19	520	3·7 (2·4–5·6)	Ref.	
Parity					
Primipara	14	281	5·0 (3·0–8·2)	1·6 (0·8–3·0)	0·154
Multipara	25	797	3·1 (2·1–4·6)	Ref.	
Marital status					
Single	4	145	2·8 (1·1–6·9)	0·7 (0·3–2·0)	0·551
Married	35	933	3·8 (2·7–5·2)	Ref.	
Education level					
Primary or less	25	640	3·9 (2·7–5·7)	1·2 (0·6–2·3)	0·540
Secondary or higher	14	438	3·2 (1·9–5·3)	Ref.	
HIV infection at enrolment or delivery					
Yes	12	214	5·6 (3·2–9·5)	1·8 (0·9–3·5)	0·082
No	27	864	3·1 (2·1–4·5)	Ref.	
Malaria infection at enrolment or follow-up					
Yes	12	210	5·7 (3·3–9·7)	1·8 (0·9–3·6)	0·070
No	27	868	3·1 (2·1–4·5)		
HIV or malaria infection at enrolment or follow up					
HIV and malaria co-infection	3	34	8·8 (3·1–23·0)	3·4 (1·0–10·9)	0·071 *
HIV infection only	9	180	5·0 (2·7–9·2)	1·9 (0·9–4·2)	0·101
Malaria infection only	9	176	5·1 (2·7–9·4)	2·0 (0·9–4·3)	0·089
Neither infection	18	688	2·6 (1·7–4·1)	Ref.	

Univariate analysis including all newborns

* p-value using Fisher's exact test

Table 4.

Adjusted prevalence ratios for congenital CMV infection by maternal characteristics, Siaya County, Kenya, November 2015–October 2017

Maternal characteristics	Model I (n=1078)		Model II (n=1066)	
	Adjusted Prevalence Ratio (95% CI)	p-value	Adjusted Prevalence Ratio (95% CI)	p-value
Age				
<25 years	0·9 (0·4–1·8)	0·674	1·0 (0·5–2·1)	0·993
≥25 years	Ref.		Ref.	
Parity				
Primipara	1·9 (0·9–4·0)	0·105	1·6 (0·8–3·5)	0·215
Multipara	Ref.		Ref.	
HIV infection				
Yes	2·1 (1·0–4·2)	0·043	2·0 (1·0–4·3)	0·056
No	Ref.		Ref.	
Malaria infection				
Yes	1·7 (0·9–3·4)	0·107	1·9 (1·0–3·7)	0·067
No	Ref.		Ref.	

Models included maternal age, parity, HIV and malaria infection at enrolment or follow-up. Model I included all newborns. Model II excluded second-born twins.