

944. Perinatal Case Fatality Rate Related to Congenital Zika Syndrome in Brazil: a Cross-Sectional Study

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Background. Many studies have demonstrated a causal link between Zika virus (ZIKV) infection, microcephaly (MCP), and other congenital abnormalities (CA). This study aimed to determine perinatal case fatality rate in cases of Congenital Zika Syndrome (CZS) in the Rio Grande do Norte State (RN), a Brazilian Northeast State highly impacted by the Zika virus outbreak.

Methods. A cross-sectional study was conducted using data obtained through the State Health Department (SHD) for cases of MCP and CA in Rio Grande do Norte from April 2015 to February 5, 2016. Definition of perinatal period: commences at 22 completed weeks (154 days) of gestation and ends seven completed days after birth.

Results. During the study period, there were 486 cases of MCP and others CA notified in RN, of which 142 were confirmed and 108 remain under investigation. The remaining 236 cases have been ruled out by presenting normal examinations or due to presenting microcephaly by noninfectious causes. Of the total confirmed cases, 26.7% (38/142) died after birth or during pregnancy. 15.78% (06/38) of confirmed deaths had ZIKV infection during pregnancy and 2.63% (01/38) had a positive TORCH blood test. The six cases related to ZIKV were confirmed by RT-PCR and/or IgM/IgG antibodies against ZIKV. The remaining cases of deaths remain either under investigation or have been ruled out.

Conclusion. This study highlights a high rate of perinatal lethality (15.78%) in cases of CZS. Despite the growing number of CZS cases, the real incidence and prevalence might be higher due to the underreporting and lack of resources for confirmatory diagnostic tests (laboratory and imaging). Due to the high rate of lethality and the ongoing uncontrolled ZIKV outbreak, this study predicts an increase in the infant mortality rate in Brazil and highlights the need for developing public health programs to control the ZIKV outbreak.

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945. Fetal and Postnatal Brain Imaging for the Detection of ZIKV Encephalopathy in the Fetus/Newborn

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Session: 121. Emerging Paradigms: Pediatric Viral Infections

Friday, October 6, 2017: 8:30 AM

Background. Up to 15% of pregnancies complicated by maternal ZIKV infection result in Zika-virus associated brain abnormalities in the fetus/newborn. Fetal ultrasound (feUS) is the standard imaging modality for the evaluation of fetal anatomy and for brain changes from congenital infection. Fetal MRI (feMRI) may be a useful adjunct.

Methods. We performed a prospective longitudinal neuroimaging study of fetuses/newborns of pregnant women with clinical and/or lab confirmed (RT-PCR and/or IgM/PRNT) diagnosis of Zika infection in Barranquilla, Colombia (endemic) and in Washington, DC, USA (travel-related). Gestational age (GA) at exposure and timing between ZIKV exposure/symptoms and imaging was documented. Subjects had one to two feMRIs and feUS, depending upon GA at enrollment. The feMRI and feUS protocols were standardized between sites and studies were centrally interpreted at Children's National. Postnatally, infants received an unseeded brain MRI and head US.

Results. Forty-eight, ZIKV exposed/infected in first or second trimester pregnant women were enrolled (46 Colombia, 2 USA). Subjects had symptoms of ZIKV infection at mean of 8.4 ± 5.7 week GA. The first feMRI and feUS were performed at 25.1 ± 6.3 week GA. Thirty-six infants had a second feMRI and feUS at 31.1 ± 4.2 week GA. Three of 48 (6%) cases had an abnormal feMRI: (1) heterotopias and abnormal cortical indent; (2) parietal encephalocele and Chiari II; (3) thin corpus callosum, dysplastic brainstem, temporal cysts, subependymal heterotopias, and generalized cerebral/cerebellar atrophy. FeUS in these three cases found (1) normal study; (2) parietal encephalocele and Chiari II; (3) significant ventriculomegaly with decreasing percentiles of head circumference from 32 to 36 week GA (38% to 3.6%). Postnatal head US revealed findings not seen on feUS: choroid plexus or germinal matrix cysts in nine infants and lenticulostriate vasculopathy in one infant.

Conclusion. feMRI and feUS provide complimentary information in the assessment of fetal brain changes in ZIKV. In cases of abnormal brain structure, feMRI reveals more extensive areas of brain damage than is seen by US. Further studies are needed to determine whether cystic changes on postnatal head US are related to ZIKV infection, or are incidental findings.

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946. Maternal Immunization with a Single-Cycle Herpes Simplex Virus (HSV) Candidate Vaccine, ΔgD-2, Protects Neonatal Mice from Lethal Viral Challenge

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Session: 121. Emerging Paradigms: Pediatric Viral Infections

Friday, October 6, 2017: 8:30 AM

Background. Perinatal HSV is associated with ~60% mortality if untreated and with substantial morbidity even with appropriate therapy. We recently engineered a single-cycle virus deleted in glycoprotein-D (ΔgD-2) that induces high-titer antibodies (Abs) that are non-neutralizing but activate the Fc receptor (FcR) to elicit antibody-dependent cellular cytotoxicity (ADCC). Immunization with ΔgD-2 completely protects adult mice from HSV-1 and HSV-2 disease following vaginal, skin, intraocular, or intranasal challenge and prevents the establishment of latency (ELife, 2014, JCI Insight, 2016). Thus we hypothesize that maternal immunization with ΔgD-2 and/or passive transfer of immune serum will protect neonates from HSV.

Methods. Four- to 6-week-old C57Bl/6 female mice were primed and boosted at 3-week intervals with ΔgD-2 or an equal volume of uninfected cell lysates (VD60 cells). Two weeks post-boost, mice were mated and pups were challenged with a lethal dose of HSV-1 (Bx31.1) at day 7 of birth. To differentiate the contribution of transplacental vs. colostrum Abs, mothers were switched at birth. Alternatively, 7-day-old mice born to nonimmunized mothers received a single dose of immune serum (400 μg total Ab) intraperitoneally at time of intranasal challenge.

Results. Thirty-eight of 47 (81%) of the pups born to and nursed by ΔgD-2-immunized mothers survived, exhibited little or no signs of disease and were protected from latency as measured by quantifying HSV DNA by PCR in neuronal tissue. In contrast, 12/14 (86%) of pups born to control vaccinated and nursed mice developed neurological signs of disease and died (P < 0.0001, Fisher's exact test). Survival was associated with increased ADCC Abs in the serum of neonatal mice. In contrast, passive transfer of immune serum, which consistently protects adult mice from infection, did not protect neonates. If newborns born to immunized mice suckled with control mice, protection was partially abrogated (11/19, 58% survival), suggesting that both systemic and mucosal Abs are required for complete protection.

Conclusion. Maternal vaccination with ΔgD-2 provides significant protection against intranasal neonatal challenge but may require exposure to systemic and mucosal Abs.

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947. Blood Viral Load (VL) Not Clinically Meaningful in Symptomatic Congenital Cytomegalovirus (cCMV) Infection

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Session: 121. Emerging Paradigms: Pediatric Viral Infections

Friday, October 6, 2017: 8:30 AM

Background. Sensorineural hearing loss (SNHL) and neurodevelopmental (ND) outcomes are favorably impacted by antiviral therapy in infants with symptomatic cCMV disease. We correlated blood VL before and during therapy with clinical findings at presentation and follow-up in this population.

Methods. Post-hoc analysis of two clinical trials conducted by the CASG from 2002 to 2013 evaluating valganciclovir therapy. 120 subjects (73 treated × 6 weeks, 47

treated × 6 months) were included. Whole blood VL was determined by real-time PCR at a central laboratory before therapy (baseline, BL) and periodically for 6 months.

Results. In subjects treated for 6 months, increases in BL VL correlated with decreased probability of better hearing outcomes at 12 months (Figure 1), but clinically meaningful VL thresholds that predict SNHL were not identified (Table 1). Subjects treated for 6 weeks had no correlation between BL VL and SNHL. No correlation was found between BL VL and Bayley ND testing at 12 and 24 months for subjects receiving either treatment duration. Subjects treated for 6 months who achieved and sustained VL suppression (<2.5 log) between treatment day 14 and month 4 had better hearing outcomes at 6, 12, and 24 months (89% vs. 56%, $P = 0.01$; 100% vs. 63%, $P = 0.0007$; 94% vs. 68%, $P = 0.04$), but 56%–68% of subjects not achieving suppression still had improved hearing. Higher BL VL correlated with BL CNS involvement, thrombocytopenia, and transaminase elevation for subjects receiving either treatment duration, but with substantial overlap in quantity of virus detected (Figure 2). Subjects with >3 symptoms of congenital CMV at presentation had higher BL VL than subjects with ≤3 symptoms (3.75 log, range 1.00–5.65, vs. 3.38 log, range 1.00–5.36; $P = 0.005$).

Conclusion. Blood VL at BL and during therapy has little clinically meaningful predictive value for long-term outcomes in symptomatic congenital CMV.

Table 1

BL VL (log genome equivalent/ml)	Hearing outcome		P-value	Negative predictive value (CI)	Positive predictive value (CI)
	Improved/protected (no.)	Others (no.)			
12 months					
>3	43	20	0.10	93 (79–100)	32 (20–43)
≤3	13	1			
>4.5	8	9	0.01	80 (70–90)	53 (29–77)
≤4.5	48	12			
24 months					
>3	42	14	0.72	83 (62–100)	25 (14–36)
≤3	10	2			
>4.5	10	5	0.32	79 (68–90)	33 (9–57)
≤4.5	42	11			

Figure 1

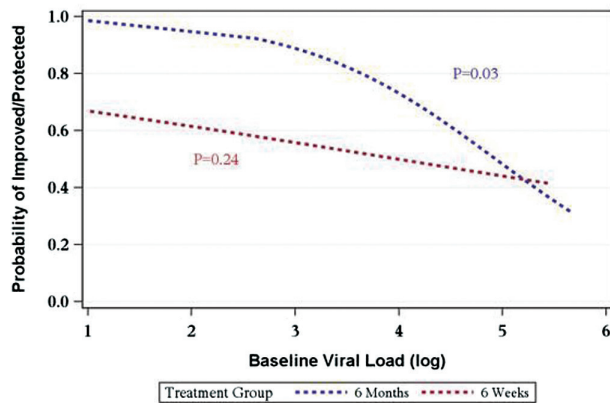
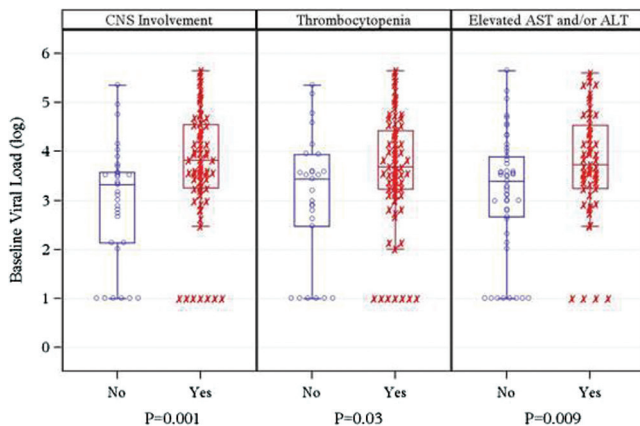


Figure 2



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948. Incidence of UL97 Resistance Mutations in Infants with Congenital Cytomegalovirus Disease Receiving 6 Months of Oral Valganciclovir Therapy
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Friday, October 6, 2017: 8:30 AM

Background. A recently completed Phase 3 randomized, controlled, double-blind, multicenter study of infants with symptomatic congenital cytomegalovirus (CMV) disease receiving 6 months of oral valganciclovir (VGCV) therapy represents the largest such population in which to evaluate treatment-emergent antiviral resistance. The most common mechanism of CMV antiviral resistance occurs through mutations in the CMV UL97 gene that confer resistance to ganciclovir (GCV). Genotypic resistance analyses were performed on infants receiving 6 months of VGCV to assess the incidence of antiviral resistance due to UL97 sequence variants.

Methods. Resistance analyses were performed by conventional DNA sequencing of the UL97 gene at multiple time points. Following CMV DNA extraction from frozen whole blood specimens, the UL97 gene was amplified with a double nested polymerase chain reaction method and sequenced to identify polymorphisms and mutations that might confer GCV resistance.

Results. Forty-six infants with symptomatic CMV disease who received a 6-month course of VGCV underwent resistance analysis to identify UL97 sequence variants. In addition to a range of natural polymorphisms known to have no effect on antiviral susceptibility, 2 subjects developed UL97 mutations known to confer resistance to GCV (A594V and G598S detected in one subject; E596G detected in another), yielding an incidence of 4%. Each of these resistance mutations occurred in specimens collected after at least 4 months of antiviral therapy. As evaluated in the original Phase 3 trial, neither of these infants showed an improvement in hearing outcome.

Conclusion. The development of treatment-emergent UL97 resistance mutations was determined in a controlled study population of infants with congenital CMV disease receiving 6 months of VGCV. This targeted resistance analysis demonstrated an incidence approaching the total incidence of antiviral resistance for CMV disease in some immunocompromised populations, such as solid-organ transplant recipients. Further studies within this study population are warranted to elucidate the risk of emerging antiviral resistance and to assess clinical impact as well as the potential need for combination antiviral therapy.

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949. Programmatic Congenital CMV Universal Screening Program

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Session: 121. Emerging Paradigms: Pediatric Viral Infections
Friday, October 6, 2017: 8:30 AM

Background. CMV is the most common congenital infection (cCMV). Traditional identification strategies including hearing screen and physical exam are insensitive and miss affected infants. To improve identification of infected newborns, we established a universal, institutional cCMV newborn screening program.

Methods. All newborns born or transferred to nurseries in a hospital system in Memphis, Tennessee between March 2016 and April 2017 were screened for cCMV. Infant saliva was collected on a Copan swab prior to discharge and within 2 weeks of birth. Specimens were centrally processed using a real-time CMV PCR assay (Simplex™ CMV) (DiaSorin, Cypress CA) amplifying the UL83 gene, and the 3M Integrated Cycler. Parents received educational materials on cCMV testing and natural history prior to specimen collection. All patients with a positive screen had a full evaluation including physical exam, eye exam, hearing testing, CBC, chemistries and head ultrasound (HUS).

Results. There were 35/6,114 (0.6%) positive screens. Of 35, 16 (45.7%) were male and 5 (14%) were less than 37 weeks gestation. Thirty-one of 35 saliva specimens were collected on day 0 or 1 of life. All patients were evaluated by an infectious disease specialist at a median of 15 days of age. Confirmatory urine PCR was positive in 25/33 (76%) tested. Overall, 11/25 (44%) with confirmed congenital CMV were symptomatic. This included 28% with microcephaly and 20% with low birth weight. Six (24%) failed newborn hearing screening of one or both ears. Other abnormalities included thrombocytopenia (5%), elevated ALT (10%), elevated direct bilirubin (5%), and abnormal HUS (11/25, 44%), of which 7/11 had lenticulostriate vasculopathy and 2/11 had intracranial calcifications. Twelve infected infants had an eye examination and none had retinitis. Eleven infants were offered therapy and five were treated. Ten of 25 congenitally infected infants had audiology follow-up by 6 months with four abnormal. All infants were referred for early intervention.