PROSPECTIVE CASE-CONTROL STUDY OF THE ASSOCIATION BETWEEN ZIKA VIRUS AND MICROCEPHALY IN BRAZIL
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Background: We previously report preliminary findings of a case-control to assess risk factors of congenital microcephaly during the first epidemic wave in the city of Recife, Northeast of Brazil. The aim is to report the characteristics of a large sample of the microcephaly cases compared to the control group and the association between microcephaly epidemic and ZIKV infection during pregnancy.

Methods: We conducted a prospective case-control study in eight public hospitals in the city of Recife, Northeast region of Brazil, Jan-Oct/2016. Cases were neonates with microcephaly classified by head circumference, gestational age and sex, using Fenton curves. Cases were defined as below the mean – 2 standard deviation (SD) and severe cases defined as those below mean -3SD. We selected two controls (neonates without microcephaly), matched by expected date of delivery and area of residence. Serum samples of cases and controls and cerebrospinal fluid samples of cases were tested for ZIKV-specific IgM and by quantitative RT-PCR. Laboratory-confirmed ZIKV infection during pregnancy was defined as positive RT-PCR result or Zika virus-specific IgM in neonates. We estimated the crude odds ratios (ORs) and 95% CIs using a median unbiased estimator for binary data using logistic regression model.

Findings: We prospectively recruited 92 microcephalic neonates (cases) and 177 controls. 66% of the cases were females versus 48% in the control group. 75% of the cases were classified as low or extreme low birth weight versus 8% of low birth weight among the controls. Among cases 34.8%(32/92) had severe microcephaly; the proportion of severe microcephaly were two times more frequent among males than females (p <0.001). In addition, 81.2% (26/32) of the severe cases were small for gestational age. Lethality rate among cases was 17.4% (16/92) considering stillbirth or death before hospital discharge. Data on ZIKV are yet not available for 10 cases. Of 82 neonates with ZIKV results; 29 (35.4%) were ZIKV positive. Severe cases
were more prone to be ZIKV positive (58.6%) compared to less severe cases (17%); risk ratio=3.5 (95% CI 1.8-6.7). Overall 35.4% of the cases and none of the controls had laboratory-confirmed ZIKV infection (OR 134.5; 95%CI 23.2 to ∞).

Interpretation: Our data shows evidence that microcephaly epidemic is a result of congenital Zika virus infection. It also confirms the strength of the association in a larger sample size.

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