More pieces to the microcephaly–Zika virus puzzle in Brazil

AP Photo/Felipe Dana

Lancet Infect Dis 2016

Published Online
September 15, 2016
http://dx.doi.org/10.1016/S1473-3099(16)30372-3

See Online/Articles
http://dx.doi.org/10.1016/S1473-3099(16)30318-8

By October, 2015, the Zika virus epidemic had grown substantially in Brazil with 14 states reporting autochthonous Zika virus transmission. Concurrently, concerns were raised regarding the discovery of a substantial increase in the number of microcephaly cases, particularly in the state of Pernambuco. The following month, a national public health emergency was declared in Brazil in response to growing concerns about the potential association between Zika virus and newborn microcephaly, with 1248 reported cases—20 times greater than the expected number.[1] Following this announcement, additional progress was made in establishing more definitive associations between Zika virus and congenital anomalies, including microcephaly.[2,3]

Studies in mouse models have addressed the causal relation between Zika virus infection in pregnancy and pathological changes in fetuses.[4,5] Although a growing body of evidence suggests that Zika virus causes brain anomalies and microcephaly, describing what has been identified as congenital Zika virus infection syndrome, there is a paucity of published prospective epidemiological studies.[3] A study by Thalia Araújo and colleagues[6] in *The Lancet Infectious Diseases* might be a missing piece to the puzzle, providing necessary epidemiological data to further advance our understanding of the association.

The investigators report preliminary findings from the first case-control study to examine the association between microcephaly and Zika virus infection, done prospectively in the metropolitan region of Recife in Pernambuco state, the hotspot of the microcephaly epidemic in Brazil. Their results highlight the striking magnitude of the association between microcephaly and laboratory-confirmed Zika virus infection: the risk is 50 times higher in all microcephaly cases and more than 100 times higher in cases with brain abnormalities detected by imaging.

However, as acknowledged by Araújo and colleagues, microcephaly remains a poorly defined disorder, and a uniform diagnostic approach is urgently needed. There is much debate in Brazil and worldwide about ascertainment of microcephaly, and the issue of disproportionate and proportionate microcephaly needs further clarification. Infants might be diagnosed with microcephaly when in fact they are globally small—ie, small for gestational age, without true isolated microcephaly.[7] This issue deserves attention, especially because in-utero growth restriction leading to the birth of small-for-gestational age infants is also a feature of congenital Zika virus syndrome.[2] Although disproportionate microcephaly has been the most publicised feature of congenital Zika virus infection, proportionate microcephaly is also identified in the setting of in-utero growth restriction caused by maternal Zika virus infection during pregnancy, not unlike other congenital infections such as cytomegalovirus. The distinction, however, is important because there might be distinct prognostic implications. Although microcephaly has been associated with poor outcome in children with congenital cytomegalovirus disease, other researchers have not found such an association. A possible source of discrepancy is failure to adjust the head size to the weight of the infant when defining microcephaly.[8]

Therefore, proportionality or lack thereof is becoming a very important parameter in ascertainment of microcephaly in Brazil. Likewise, categorising patients according to the presence of microcephaly and other CNS abnormalities as detected by brain imaging can enable the stratification of patients into varying levels of disability risk.

As our knowledge of the clinical repercussions of congenital Zika virus infection advances, it becomes apparent that microcephaly is only one possible adverse outcome among a range of disorders that might be part of congenital Zika virus syndrome. A population-level increase in CNS anomalies was observed in French Polynesia and in Brazil. More data are needed to refine gestational age-specific risk estimates for microcephaly and other adverse outcomes related to Zika virus infection.[9] Therefore, even though the modified Fenton curve[10] or the Intergrowth score[11] provide useful prognostic information, a full clinical assessment of the infant with clinical follow-up should provide more accurate information over time.

As definitions shift and more information is gathered about the pathogenesis and clinical manifestations of Zika virus congenital disease, it is important that surveillance efforts monitoring the current epidemic continue to critically evaluate their data. Newly

identified clinical and phenotypic criteria should be further analysed, also taking into account findings from imaging studies. This approach will help establish a more definitive gold standard case definition and improve our understanding of the clinical manifestations of congenital Zika virus infection.

Patricia Brasil, Karin Nielsen-Saines
Fiocruz RJ, Rio de Janeiro, 22010122, Brazil (PB) and Department of Pediatrics, UCLA, Los Angeles, CA, USA (KNS)
patricia.brasil@ini.fiocruz.br

We declare no competing interests.

1 Brasil Ministério da Saúde. Informe Epidemiológico N°1/2015—Semana Epidemiologica 46—Monitoramento dos casos de microcefalias no Brasil. 2015. http://portalsaude.saude.gov.br/images/pdf/2015/novembro/24/COES-Microcefalias---Informe-Epidemiol--gico---SE-46---24nov2015.pdf (accessed Aug 25, 2016).

2 Brasil P, Pereira Jr J, Raja Gabaglia C, et al. Zika virus infection in pregnant women in Rio de Janeiro—preliminary report. *N Engl J Med* 2016; published online March 4. DOI:10.1056/NEJMoa1602412.

3 Rasmussen SA, Jamieson DJ, Honein MA, Petersen LR. Zika virus and birth defects—reviewing the evidence for causality. *N Engl J Med* 2016; **374:** 1981–87.

4 Miner JJ, Cao B, Govero J, et al. Zika virus infection during pregnancy in mice causes placental damage and fetal demise. *Cell* 2016; **165:** 1081–91.

5 Cugola FR, Fernandes IR, Russo FB, et al. The Brazilian Zika virus strain causes birth defects in experimental models. *Nature* 2016; **534:** 267–71.

6 Araújo TVB, Rodrigues LC, Ximenes RAA, et al. Association between Zika virus infection and microcephaly in Brazil, January to May, 2016: preliminary report of a case-control study. *Lancet Infect Dis* 2016; published online Sept 15. http://dx.doi.org/10.1016/S1473-3099(16)30318-8.

7 von der Hagen M, Pivarcsi M, Liebe J, et al. Diagnostic approach to microcephaly in childhood. *Dev Med Child Neurol* 2014; **56:** 732–41.

8 Noyola DE, Demmler GJ, Nelson CT, et al. Early predictors of neurodevelopmental outcome in symptomatic congenital cytomegalovirus infection. *J Pediatr* 2001; **138:** 325–31.

9 Johansson MA, Mier-y-Teran-Romero L, Reefhuis J, Gilboa SM, Hills SL. Zika and the risk of microcephaly. *N Engl J Med* 2016; **375:** 1–4.

10 Fenton TR, Kim JH. A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. *BMC Pediatr* 2013; **13:** 59.

11 Villar J, Ismail LC, Victora CG, et al. International standards for newborn weight, length, and head circumference by gestational age and sex: the Newborn Cross-Sectional Study of the INTERGROWTH-21st Project. *Lancet* 2014; **384:** 857–68.