CORRESPONDENCE

Neurodevelopment in Infants Exposed to Zika Virus In Utero

TO THE EDITOR: During the Zika virus (ZIKV) epidemic in Rio de Janeiro from September 2015 through June 2016, a prospective cohort study involving symptomatic pregnant women who had ZIKV infection confirmed by reverse-transcriptase–polymerase-chain-reaction assay was established.[1] The study was approved by the institutional review boards at Fundação Oswaldo Cruz in Rio de Janeiro and the University of California, Los Angeles, and all the women provided written informed consent for themselves and their children.

A total of 182 children who were exposed to ZIKV in utero were followed longitudinally with specialized testing (Fig. S1 in the Supplementary Appendix, available with the full text of this letter at NEJM.org). Of these children, 131 (72%) were brought by their parents for at least one of the following evaluations: brain imaging (in 115 children), complete eye examinations (in 112),[2] assessment with the Bayley Scales of Infant and Toddler Development, third edition (Bayley-III)[3] (in 104), and assessment of brain-stem auditory evoked response (in 49). Brain-imaging studies consisted of transfontanelle cerebral ultrasonography (in 98 children), computed tomography (in 25), magnetic resonance imaging (MRI) (in 47), or all of these tests; 45 children who underwent brain imaging (39%) underwent more than one type of study. Transfontanelle cerebral ultrasonography was usually performed first, and further imaging was performed according to clinical discretion.

Trained personnel assessed 104 children who were between 12 months and 18 months of age and who had similar socioeconomic backgrounds. Bayley-III, a developmental tool validated cross-culturally in Brazil,[4] was used to assess three domains (cognitive, language, and motor functions). A total of 94 children underwent both Bayley-III and neuroimaging assessments. Abnormal findings on neuroimaging were identified in 39 of 115 children (34%) overall and in 35 of 94 children (37%) who also underwent neuropsychological testing. Among 94 children who underwent both neuroimaging and Bayley-III testing, neuroradiologists found that 10 (11%) had structural abnormalities, 5 (5%) had nonstructural abnormalities, and 20 (21%) had abnormal results that were limited to a nonspecific T_2-weighted hypersignal on MRI.

As shown in Figure 1, and in Table S1 in the Supplementary Appendix, of the 94 children who had undergone neuroimaging and Bayley-III testing, 59 (63%) had Bayley-III scores above 85 for all three domains (1 SD below the mean [±SD] score of 100±15 [scores range from 55 to 145, with lower scores indicating a greater degree of developmental delay]); 24 (26%) had one or more Bayley-III scores between 85 and 71 (1 to 2 SD below the mean [±SD] score); and 11 (12%) had one or more scores below 70 (2 SD below the mean [±SD] score). No microcephaly was detected and findings on brain imaging were normal in 44 children (47%) with Bayley scores higher than 85, in 13 (14%) with scores between 85 and 71, and in 2 (2%) with scores of 70 or

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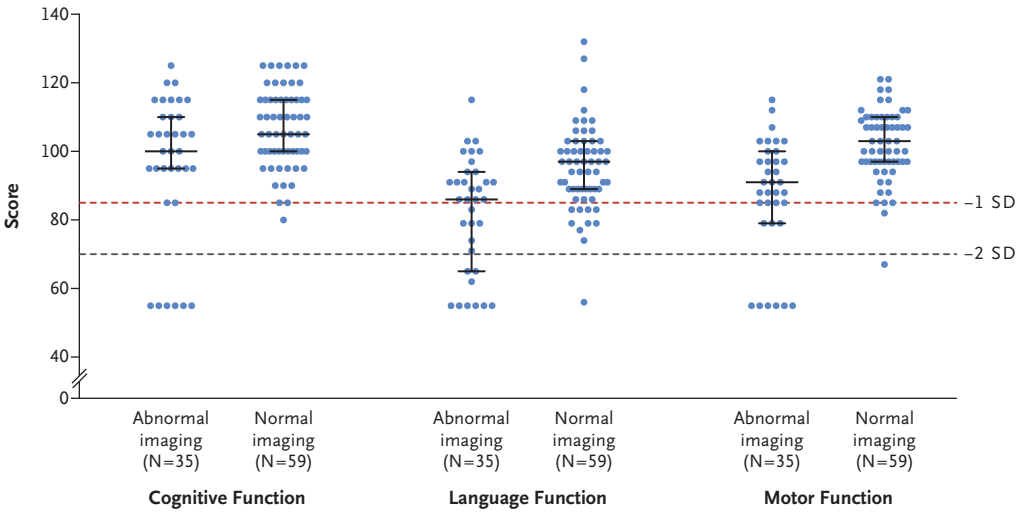

Figure 1. Individual Scores on the Bayley-III Scales at 12 to 18 Months of Age, According to Neuroimaging Results.

Shown are the scores for cognitive, language, and motor functions on the Bayley Scales of Infant and Toddler Development, third edition (Bayley-III). Standard scores on the Bayley-III scales range from 55 to 145, with higher scores indicating more advanced development; the mean (±SD) score is 100±15, and a score of less than 85 indicates a developmental delay and a score less than 70 indicates severe developmental delay. The scores of 94 children who had in utero exposure to Zika virus are indicated by circles. The solid horizontal lines represent median values, and the I bars interquartile ranges.

less in any domain. Conversely, results of brain imaging were abnormal in 15 children (16%) with Bayley-III scores higher than 85, in 11 (12%) with scores between 85 and 71, and in 9 (10%) with scores of 70 or less in any domain.

Children with normal brain imaging were 20% less likely to have a Bayley-III score that was 2 SD below the mean (±SD) score than those with abnormal brain imaging (odds ratio, 0.80, 95% confidence interval, 0.70 to 0.91). Among children with abnormal findings on brain imaging, 7 of 112 (6%) had an abnormal eye examination and 6 of 49 (12%) had an abnormal hearing assessment. Among 131 children who were exposed to ZIKV in utero and who underwent imaging, neurodevelopmental assessment, sensory organ assessment, or all of these tests, 19 (14%) were found to have severe neurodevelopmental delay (2 SD below the mean [±SD] score), sensory organ dysfunction, or both; this rate is higher than that reported in previous studies.[5] Although a significant association was noted between normal results on brain imaging and higher Bayley-III scores, neuroimaging did not predict developmental delay in 2% of children and normal development in 16% of children.

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Mutation Clearance after Transplantation for Myelodysplastic Syndrome

TO THE EDITOR: Duncavage and colleagues (Sept. 13 issue)[1] address the molecular predictors of disease progression and survival among patients with myelodysplastic syndrome (MDS) who underwent allogeneic hematopoietic stem-cell transplantation. With the use of enhanced exome sequencing, they found that detection of at least one mutation with a maximum variant allele frequency of at least 0.5% at day 30 after transplantation was associated with a higher risk of progression than the absence of such a mutation.

The article offers a new perspective on the understanding of the biologic properties of MDS that may be further explored in the context of the unique immunologic milieu observed after transplantation. In fact, it is well known that most of the therapeutic efficacy of allogeneic hematopoietic stem-cell transplantation relies on the graft-versus-leukemia effect,[2] which is also observed in patients with MDS[3] and which often occurs in parallel with graft-versus-host disease (GVHD). In this context, it would be crucial to