1. Case Records of the Massachusetts General Hospital (Case 41-2015). N Engl J Med 2015;373:2664-76.
2. Lipsker D. Clinical examination and differential diagnosis of skin lesions. Paris: Springer-Verlag France, 2013.

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THE DISCUSSANTS REPLY: Lipsker questions the relevance of performing molecular testing in the evaluation for dyskeratosis congenita. However, we would like to emphasize the importance of telomere-length testing by means of flow cytometry combined with fluorescence in situ hybridization in the evaluation of this patient. More than 90% of patients with short telomeres do not have the classic mucocutaneous features that define dyskeratosis congenita, and thus the condition may not always be recognized clinically.[1] In such cases, pulmonary fibrosis, emphysema, liver disease, and aplastic anemia are the first manifestations.[1,2] In this patient, leukoplakia and hyperpigmentation appeared during late childhood, and these features were absent in his affected uncle during adulthood.

The classic features of dyskeratosis congenita were described in the early part of the 20th century[3]; however, recent advances indicate that their presence is neither sensitive nor specific. For example, patients with other genodermatoses, such as the Rothmund–Thomson syndrome, may have these features but in the presence of normal telomere length.[4] The term "short-telomere syndrome" has been used to reflect the broad spectrum of disorders that share causative defects in telomere maintenance.[1] Since the diagnosis of a short-telomere syndrome informs patient care, measurement of telomere length, along with evaluation of the telomerase and telomere genes, is emerging as a practice in patients suspected to have short-telomere disorders.[5]

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1. Armanios M. Syndromes of telomere shortening. Annu Rev Genomics Hum Genet 2009;10:45-61.
2. Stanley SE, Chen JJ, Podlevsky JD, et al. Telomerase mutations in smokers with severe emphysema. J Clin Invest 2015;125:563-70.
3. Walne AJ, Dokal I. Dyskeratosis congenita: a historical perspective. Mech Ageing Dev 2008;129:48-59.
4. Walne AJ, Vulliamy T, Beswick R, Kirwan M, Dokal I. Mutations in C16orf57 and normal-length telomeres unify a subset of patients with dyskeratosis congenita, poikiloderma with neutropenia and Rothmund-Thomson syndrome. Hum Mol Genet 2010;19:4453-61.
5. Armanios M. Telomeres and age-related disease: how telomere biology informs clinical paradigms. J Clin Invest 2013;123:996-1002.

DOI: 10.1056/NEJMc1601156

Computed Tomographic Findings in Microcephaly Associated with Zika Virus

TO THE EDITOR: Zika virus (ZIKV) is a mosquito-borne flavivirus that is transmitted primarily by *Aedes aegypti* mosquitoes.[1] Starting in May 2015, an outbreak of ZIKV infection has been reported in Brazil in association with an increasing number of neonates with congenital microcephaly in ZIKV-affected regions.[1] In these areas, the prevalence of congenital microcephaly increased by a factor of 20 over the prevalence before the outbreak.[1] ZIKV RNA has been identified in the brain of a fetus with congenital microcephaly.[2] In addition, ZIKV RNA was identified in the amniotic fluid of two women whose fetuses had congenital microcephaly detected on prenatal ultrasonography.[1] These events and observations prompted concern about the possible association between congenital microcephaly and the recent outbreak of ZIKV infection in Brazil.[3] Only limited imaging data about the brain anomalies that may be associated with intrauterine ZIKV infection are available.

We report findings obtained by means of head computed tomography (CT) in 23 infants (13 female) with congenital microcephaly in which the clinical and epidemiologic data are compatible with congenital ZIKV infection in the Pernambuco state of Brazil. Head CTs were obtained for clinical reasons between September and Decem-

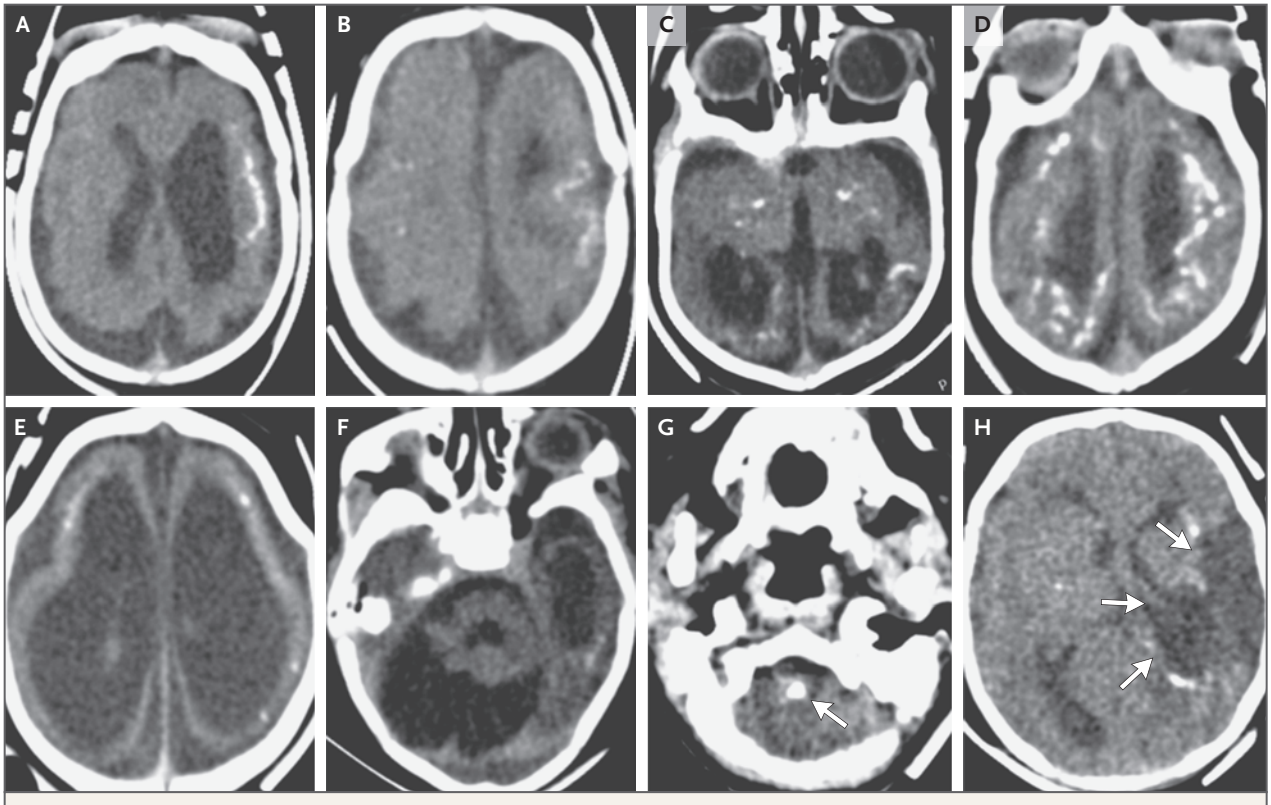

Figure 1. Computed Tomography in Eight Infants with Congenital Microcephaly.

Axial computed tomographic (CT) images of the heads of eight infants who were born with congenital microcephaly associated with intrauterine ZIKV infection show calcifications in bandlike distributions (Panels A, B, and D) with isolated configurations (Panels B, C, E, and G), punctate configurations (Panels B and E), and larger configurations (Panels A, C, D, and G) at the level of the corticomedullary junction (Panels A, B, and D) within the frontal, parietal, and temporal lobes, basal ganglia (Panel C), and upper cervical spinal cord (Panel G, arrow). In addition, there are visible signs of global cortical hypogyration (Panels A through F and H), moderate-to-severe ventriculomegaly (Panels A and C through F), severe global cerebellar hypoplasia (Panel F), abnormal hypodensity of the supratentorial white matter (Panels A, B, D, and H), and encephalomalacic changes after ischemic stroke in the vascular territory of the left middle cerebral artery (Panel H, arrows).

ber 2015. Samples of cerebrospinal fluid were available for serologic testing in 7 of the 23 infants, and results on enzyme-linked immunosorbent assay for ZIKV IgM antibody were positive in all 7 samples. Findings on serologic analysis regarding TORCH infection (toxoplasmosis, other [syphilis, varicella, parvovirus, and human immunodeficiency virus], rubella, cytomegalovirus, and herpes simplex) were negative in all 23 infants.

Head CT images were obtained at a mean age of 36 days after birth (range, 3 days to 5 months). Intracranial calcifications were seen in all the infants and mainly involved the frontal lobe (in 69 to 78% of the infants) and the parietal lobe (in 83 to 87%) (Fig. 1). The calcifications were located mainly at the corticomedullary junction (in 53 to 86%). The configuration of the calcifications was mostly punctate (in 72 to 100%), with a predominately bandlike distribution (in 56 to 75%). The calcifications were seen in the basal ganglia (in 57 to 65%) and in the thalamus (in 39 to 43%). Ventriculomegaly was found in all the infants and was rated as severe in the majority (53%) and involving only the lateral ventricles in 43%. All the infants had global hypogyration of the cerebral cortex that was severe (only the Sylvian fissure was obviously present) in 78% of the infants. Cerebellar hypoplasia was present in 17 of the infants (74%) and involved

only one cerebellar hemisphere in 3 infants. In 2 infants, the brain stem was globally hypoplastic. In all the infants, there was abnormal hypodensity of the white matter, and in 87% of the patients it diffusely involved all the cerebral lobes. In 1 infant, chronic encephalomalacic changes from ischemic stroke in the vascular territory of the left middle cerebral artery were seen.

Intrauterine ZIKV infection appears to be associated with severe brain anomalies, including calcifications, cortical hypogyration, ventriculomegaly, and white-matter abnormalities, although we cannot determine with certainty when ZIKV infection may have occurred during fetal development in these 23 infants. Our findings are nonspecific and may be seen in other congenital viral infections. The global presence of cortical hypogyration and white-matter hypomyelination or dysmyelination in all the infants and cerebellar hypoplasia in the majority of them suggest that ZIKV is associated with a disruption in brain development rather than destruction of brain. The neuronal and glial proliferation as well as neuronal migration appear to be affected. The mothers of the microcephalic infants in our study population had symptoms (e.g., low-grade fever and cutaneous rash) that were compatible with ZIKV infection during the first or second trimester of pregnancy, similar to the findings in other studies.[4] Tang et al. found that ZIKV directly infects human cortical neural progenitor cells with high efficiency, resulting in stunted growth of this cell population and transcriptional dysregulation.[5] This observation supports the type of disruptive, anomalous brain development that we found in these infants.

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Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

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1. Zika virus spreads to new areas — region of the Americas, May 2015–January 2016. MMWR Morb Mortal Wkly Rep 2016;65:55-8.
2. Mlakar J, Korva M, Tul N, et al. Zika virus associated with microcephaly. N Engl J Med 2016;374:951-8.
3. Possible association between Zika virus infection and microcephaly — Brazil, 2015. MMWR Morb Mortal Wkly Rep 2016;65:59-62.
4. Oliveira Melo AS, Malinger G, Ximenes R, Szejnfeld PO, Alves Sampaio S, Bispo de Filippis AM. Zika virus intrauterine infection causes fetal brain abnormality and microcephaly: tip of the iceberg? Ultrasound Obstet Gynecol 2016;47:6-7.
5. Tang H, Hammack C, Ogden SC, et al. Zika virus infects human cortical neural progenitors and attenuates their growth. Cell Stem Cell 2016 March 4 (Epub ahead of print).

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Evidence of Sexual Transmission of Zika Virus

TO THE EDITOR: Zika virus (ZIKV), an emerging flavivirus, generally causes mild infection in humans but is associated with severe neurologic complications and adverse fetal outcomes. ZIKV is transmitted to humans primarily by aedes mosquitoes. However, there is some evidence of sexual transmission.[1,2] Two studies have shown the presence of infectious ZIKV in semen.[3] A recent article described detection of ZIKV RNA in semen 62 days after the onset of illness, but infectious virus was not cultured.[4]

We report a case of ZIKV infection in a previously healthy 24-year-old woman (Patient 1) who was living in Paris and in whom acute fever, myalgia, arthralgia, and pruritic rash developed on February 20, 2016. She was not receiving any medication, had not received any blood transfusions, and had never traveled to a region where