Zika and microcephaly: causation, correlation, or coincidence?

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Commentary

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In November, the Brazilian Ministry of Health released a report declaring a dramatic rise in the number of microcephaly cases, particularly in the Pernambuco state [1]. Although a definitive cause was not declared, the Ministry suggested an association with Zika virus infection. This was a bold move by the government and raised the question as to whether Zika caused this condition, correlated with it, or had no involvement at all other than coincidence. At the time, no concrete answers were available casting a shadow on the statement and the government. Yet, based on previous studies on the virus and the mechanism behind microcephaly, the claim might not be entirely irrational.

Zika virus is a member of the *Flaviviridae* family, which includes Dengue and West Nile Virus. Vertical transmission of Dengue [2] has been demonstrated resulting in infection and a risk for death. In contrast, perinatal transmission of WNV [3] has not been observed as only cord blood antibodies have been detected. In Brazil, Zika viral RNA has been detected both in the mothers and amniotic fluid samples from the fetuses. Thus, Zika virus may have the potential to infect the fetus and potentially cause neurodevelopmental dysfunction including microcephaly.

The pathological properties of Zika were first described in 1952, when Dick et al. [4] demonstrated viral tropism to the brain in intraperitoneally infected mice and an increase in viral titres over several days. This research suggested the virus could cross the blood brain barrier. The research findings were complemented in 1972 by Bell and colleagues [5] who observed the progression of disease in directly infected mouse brains. Based on their observations, the virus infected both neurons and glia, producing a variety of intracytoplasmic inclusions, which they termed, “virus factories.” These factories originated from the endoplasmic reticulum and associated with other organelles including the nucleus and the mitochondria.
Those microscopic observations describe what we now know as autophagy. As discussed by Travassos and Carneiro in this issue, this cellular process is designed to ensure cell homeostasis through entrapment and eventual degradation of unwanted cellular material. This mechanism is also used to combat viral infection although the efficiency is varied as a result of viral regulatory mechanisms [6]. In the case of flavivirus infection [7], for example, interactions between the virus and the Endoplasmic Reticulum induce autophagy. Yet these viruses prevent completion of the autophagy process, flux [8], providing a perfect environment for the creation of “viral factories” to maximize viral replication and amplification.

Although autophagy has not been described in Zika-infected neural cells, experimentally-infected skin fibroblasts [9] have shown autophagy does occur and the virus hijacks this biological process for replication. This provides some evidence to support the involvement of Zika virus in other cell lineages, including as seen by Bell et al [5], neural cells. This also offers a potential path to determining whether the virus is directly, indirectly, or not involved in the development of microcephaly.

One of the causes of microcephaly involves abnormal function of centrosomes [10]. Although normally associated with mitosis, these organelles are also involved in other cellular processes including migration, polarity and proper trafficking of vesicles. In reference to microcephaly [11], amplification of centrosome number has been revealed to be one of the inducers of this condition. Certain proteins have a dual role in autophagy as well as centrosome stability. One particular example is ultraviolet (UV) irradiation resistance-associated gene (UVRAG). It is involved in initiation and maturation of autophagosomes [12] as well as centrosome and chromosome stability [13]. Another is Beclin-1, which plays an integral role in autophagy and is known to contribute to chromosomal stability in cancer cells [14]. In the context of neural brain
development, an increase in centrosomes in mice [11] results in a delay in mitosis, an increase in apoptosis, improper neural stem cell orientation, premature neuronal differentiation, and a decrease in progenitor cells. The overall effect reduces the formation of brain matter leading to the reduced brain size indicative of microcephaly.

Although the mechanisms of Zika virus pathogenesis appear to fall in line with the requirements for centrosome abnormalities, there is as of yet no evidence to prove culpability. Future studies need to be performed in order to establish and solidify this link. In particular, vertical transmission of Zika virus needs to be concretely demonstrated as well as any direct or indirect effects of infection on neural development. Furthermore, studies should explore other aberrations in fetal development apart from microcephaly. This is an important consideration since the roles of proper centrosome segregation, chromosomal stability, and autophagy are not restricted to neural development suggesting other possible sequelae may be possible.

References:


