New cerebral findings in infants with congenital Zika syndrome
Calcification that resolves sets Zika apart from other congenital infections

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Since the first outbreak of Zika virus infection in Uganda in 1947, the world has dealt with sporadic repeated outbreaks. But the most recent one in Brazil in 2015 was different. It appeared to be associated with an increased incidence of microcephaly among infants born to mothers infected with the virus during gestation, especially during the first trimester.

A series of seminal research papers convincingly correlated the presence of microcephaly with congenital Zika virus infection. The authors all described subcortical calcifications, abnormal development of central nervous system neurons, cortex, and white matter; and associated ventriculomegaly in affected infants. These findings were identified by both histopathological analyses and non-invasive neuroimaging.

In this issue, Aragao and colleagues report new and important findings in the central nervous system on follow-up computed tomography (CT) scans from a series of 37 infants with confirmed or probable congenital Zika syndrome. Comparison of scans done soon after birth with follow-up scans done about one year later showed persistent evidence of cortical and white matter developmental abnormalities and subcortical calcifications, along with continued evolution of generalised cerebral volume loss and worsening ventriculomegaly. Microcephaly persisted in all infants.

Perhaps more importantly, the authors report a surprising decrease in the overall number and size of subcortical calcifications at one year follow-up, which did not correlate with the degree of cerebral volume loss. Calcifications reduced in 34 infants, and, remarkably, disappeared altogether in one. These findings suggest that the sequelae of this strain of congenital Zika virus may be different from those of most other congenital infections (such as cytomegalovirus, herpesvirus, otherwise known as STORCH infections) in which bulky calcifications are often permanent.

The authors’ longitudinal prospective study design allows within-person comparison of neuroimaging findings and helps characterise the clinical course of congenital Zika syndrome, at least with respect to the appearance of cerebral pathology on non-invasive imaging.

However, there are at least three important caveats to consider. Firstly, this is a relatively small case series of just 37 infants, and confirmation is required. Secondly, these findings may be specific to the particular strain of Zika virus found in this region of Brazil, so the generalisability of the findings is unclear. Finally, as the authors state, none of the infants had follow-up magnetic resonance imaging scans, which limits a more detailed evaluation of the structural changes that may have occurred during follow-up. We are limited by the resolution and sensitivity of CT imaging (eg, we cannot tell whether these infants developed axonal changes).

Despite these caveats, the authors’ intriguing findings will undoubtedly inspire more research to further characterise structural changes associated with the Brazilian strain of Zika virus and also to understand the underlying pathophysiological basis for these changes.

The authors report an intriguing hypothesis for their findings, informed by histological analyses of autopsy specimens from fetuses who died during different Zika outbreaks in Slovenia and Washington DC in the US. The specimens showed no evidence of inflammatory histological changes. Laboratory research in human cells and animal models also supports a non-inflammatory pathological mechanism of neuronal loss after Zika infection, and the authors hypothesise that the process involves non-inflammatory induced apoptosis of neuroprogenitor cells followed by phagocytosis by microglia (the brain’s scavenger cells). They propose that calcium deposits are reduced by the same phagocytic process.

Recent reports have described a non-inflammatory mechanism of neuronal injury for strains of Zika virus found in Asia, although these authors also suggest that a strain found in Africa may induce neuronal cell death through a classic inflammatory mechanism.

The pathophysiological hypothesis of Aragao and colleagues should encourage further research into the target cells affected.
and host’s immune responses after gestational infections with the Brazilian strain of Zika virus. Their description of decreasing or complete resorption of calcifications in affected infants suggests that this imaging characteristic may be what sets congenital Zika syndrome apart from other congenital STORCH infections. Any implications for clinical improvement remain unclear.

For now, the most important conclusion from this study is that absence of subcortical calcifications on non-invasive neuroimaging should not be used to rule out a diagnosis of congenital Zika syndrome.

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