MedicalXpress

Zika virus identified in brain and placenta tissue, strengthening link to birth defects

June 30 2016

New research, published today in *The Lancet*, reveals that Zika virus has been detected in the brain tissue of a deceased 2-month-old baby in Brazil who was diagnosed with microcephaly, in the brain tissue of two newborns who died shortly after birth, and in the placenta tissue of two foetuses that were spontaneously aborted.

The small study provides further evidence that Zika virus infection in the first trimester of pregnancy can result in placental and foetal damage and loss, and early insight into the effect of Zika virus infection on foetuses. Further studies are now needed to understand the exact mechanism of transmission.

Since the start of the Zika virus outbreak in Brazil in March 2015, there have been 7,343 cases reported cases of microcephaly, of which 1,271 have been confirmed. Fifty-seven of the microcephaly cases were fatal.

In this paper, Dr Sherif R. Zaki from the Division of High Consequence Pathogens and Pathology (DHCPP), Centers for Disease Control and Prevention, Atlanta, USA, and colleagues, analysed tissues from three post-mortem cases and two placentas. All five mothers reported symptoms of Zika virus infection during the first trimester of pregnancy. In three cases (two newborns who died within hours of being born, and one who died at two months), microcephaly was detected during pregnancy or at birth. The two other cases were foetuses spontaneously aborted at 11 and 13 weeks gestation.

In the three fatal cases, Zika virus antigens were detected in the neurons and glial cells. Analysis of brain tissue showed damage and degeneration of cells, microcalcification (calcium deposits), and cell death. The authors say that the absence of a substantial inflammatory response in the brain and any specific structural effects appear to distinguish Zika virus infection from other infections, such as herpes, that are associated with microcephaly.

No evidence of Zika virus was detected outside the central nervous system in the heart, liver, spleen, kidney or cartilage. All three cases showed a range of birth defects, including craniofacial malformations and a range of brain abnormalities.

Zika virus antigens were also detected in the placental tissue of the two aborted cases. Tests on all five cases were negative for the presence of dengue virus antibodies and tested negative for other infections including rubella virus, *Toxoplasma gondii*, and herpes. Genetic analysis of the Zika virus samples showed the greatest match to strains isolated in Brazil during 2015.

The authors say that the mechanism by which Zika virus may cause abnormalities is not yet understood, but that it's likely the result of the virus attacking the nervous system with subsequent damage to the brain and muscle impairment.

"There are a number of viral infections, including herpes and rubella, which are known to cause birth defects, especially if infection occurs in the first trimester of pregnancy. But, until now, there have been no reports of a mosquito-borne virus that could cause severe birth defects," says lead author Dr Zaki. "Zika virus is an evolving epidemic, and many important questions remain to be explored. We are continuing to investigate the possible spectrum of neurological defects in infants and various abnormalities in placental tissues, and further studies will now

need to look at whether there is a link between birth defects and Zika virus infection during the second and third trimester of pregnancy, and understand the mechanism of transmission."

Writing in a linked Comment, Dr Drucilla J Roberts from the Massachusetts General Hospital, Department of Pathology, Boston, MA, USA, and Dr Matthew P Frosch from the C S Kubik Laboratory for Neuropathology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA, say: "Although the US Centers for Disease Control and Prevention has concluded that Zika virus causes microcephaly and other foetal brain defects, demonstration of Zika virus in tissues is sparse...Additional detailed pathological studies are needed to properly elucidate the full spectrum of congenital Zika syndrome. Work remains to confirm Zika virus infection as causal in perinatal complications and should include histopathological examination of available tissues at various gestational ages. This report highlights that we can learn much about the pathogenesis of Zika virus congenital infection through careful pathological investigation, but leaves us with many questions for study."

More information: *The Lancet*, www.thelancet.com/journals/lan … (16)30883-2/abstract

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