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Mechanisms of Zika Virus-Induced Microcephaly in Utero

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ABSTRACT

The association between Zika virus (ZIKV) infection in pregnancy and foetal microcephaly remains incompletely understood despite intense research interest. This review aimed to evaluate proposed mechanisms by which ZIKV might impair neurodevelopment and to assess how convincingly current evidence supports a causal relationship. Studies published since 2005 were identified through structured database searches using predefined inclusion and exclusion criteria, focusing on human, in vitro and animal models that examined ZIKV neurotropism, placental transmission and foetal brain outcomes. Evidence consistently shows that ZIKV exhibits marked neurotropism, preferentially infecting neural progenitor cells, disrupting proliferation and inducing cell death in developing brain tissue. Murine and organoid models further demonstrate cortical thinning and reduced brain volume following congenital exposure, broadly mirroring clinical microcephaly phenotypes. However, heterogeneity in experimental design, viral strains, timing and dose of infection, and outcome measures limits direct comparison across studies and weakens causal inference. Overall, current data strongly suggest that ZIKV can contribute to microcephaly, but they do not yet delineate a single, definitive pathogenic pathway. More integrative, longitudinal research across epidemiological, clinical and mechanistic domains is needed to clarify risk, refine causal models and inform the development of any future preventive or therapeutic strategies.

KEYWORDS: congenital infection, foetal neurodevelopment, microcephaly, teratogenic mechanisms, zika virus.

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INTRODUCTION

Zika virus (ZIKV) is a notable re-emerging pathogen that is gaining attention due to its potential to cause severe complications. (1) It is an arthropod-borne (2), flavivirus that is transmitted in humans by Aedes aegypti mosquitoes. ZIKV is a tropical and subtropical pathogen. Its primary clinical manifestations include low fever, and headache, which can progress to more severe complications like microcephaly. (1)

After the Zika virus was identified in 1947, there were few cases reported in humans. Since then, ZIKV outbreaks have been reported in Africa, Southeast Asia and Southern America. However, in 2015, over 2000 cases linked ZIKV to cases of microcephaly in infants with neurological disorders. (4)

Microcephaly refers to a head circumference at least two standard deviations below the mean for respective gender and age. This can be caused by abnormalities in brain development preventing the brain from reaching its full size or sudden hindrance of brain growth. Genetic and metabolic disorders, prenatal, perinatal, postnatal injuries and infections like ZIKV can cause both congenital and postnatal microcephaly. (5)

As ZIKV has no cure, understanding how ZIKV may be contributing to microcephaly diagnoses will help with prognosis and reduce spread. Some studies deduce that there is a causal association between ZIKV infection (6), however, most studies have evaluated that there is a strong association between the diagnosis of the infection and the condition. (2) A review that evaluated the risk of developing microcephaly with Zika virus concluded a strong correlation. (3) While such studies indicate a strong correlation between ZIKV infection and microcephaly, the underlying mechanisms remain poorly understood. Hence, this review aims to investigate the possible mechanisms by which ZIKV infection may manifest itself in foetuses and induce microcephaly.

METHOD

To search for relevant literature, the databases TRIP, PubMed and Medline were used. Keywords used were: “Zika virus”, ‘ZIKV’, ‘microcephaly’, and ‘Zika induced microcephaly’. These terms were combined with ‘AND’ to find literature that contained both phrases as well as ‘OR’ to broaden searches. Once discussion themes had been chosen, searches were refined for example, ‘ZIKV and immune response’. Any articles that did not specifically include ZIKV were excluded as well as articles that predated the year 2005. Other resources were found utilizing backward and forward citation searching. (Figure 1) portrays the detailed search method.

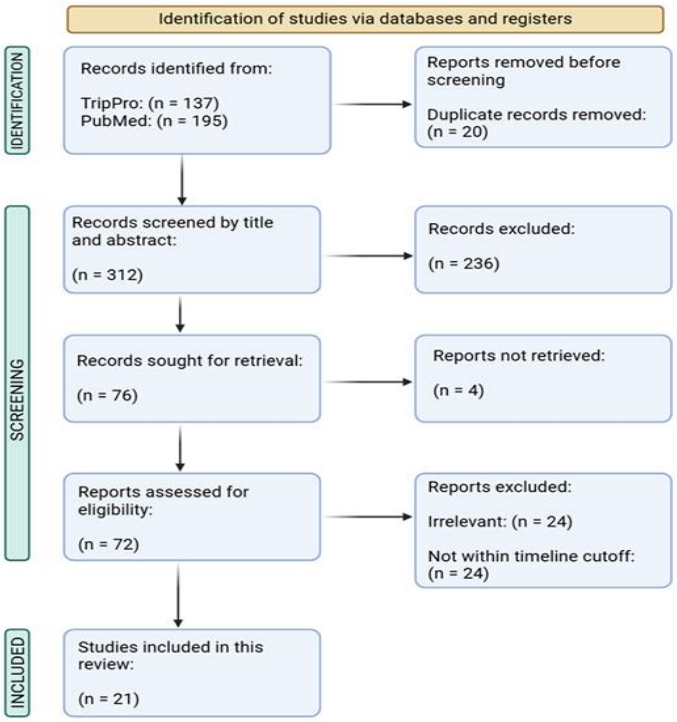

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Fig 1: A PRISMA diagram that visualises the methods used to collect research

This figure is referred to in the methods section of this report. It has been adapted from: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021 Mar 29; n71.

DISCUSSION

A. Neural Progenitor Cell Infection

Research has revealed that pathogens like ZIKV predominantly target neural progenitor cells (NPC). (7) Investigation into the initial progression of the ZIKV showed that it spread in the NPC by contact with an infected cell. This aids our understanding of how the infection propagates and causes symptoms. (8) It has been suggested that ZIKV infections cause NPC cycle arrest which in turn increases cell mortality. (5) A review of studies presents interconnected theories on how pathway inhibition and gene expression contribute to ZIKV-induced microcephaly.

An investigation into foetal NPC's showed how the ZIKV has Non-structural Protein 4A and 4B (NS4A and NS4B) proteins which block a crucial signalling pathway in humans, inducing autophagy, the conserved degradation of the cell. (9) The phosphatidylinositol 3-kinase mammalian target of the rapamycin (PI3K–AKT–mTOR) signalling pathway is an integral regulator of cell growth and proliferation. (10) An examination of the pathway suggested that the ZIKV replication and protein expression in the body led to the suppression of Akt phosphorylation at Thr308 and Ser473, which subsequently led to reduced mTOR phosphorylation. This would minimize cerebral production efficiency due to increased autophagy and decreased proliferation. (9) Further study of the virus's genome showed that the expression of Non-structural Protein 2A (NS2A) also led to a significant reduction in the proliferation of NPC by triggering premature neurogenesis, included in the same pathway. (11)

A study that investigated the molecular fingerprint of ZIKV after infection to a human iPS-derived NPC demonstrated modulation of multiple cell pathways in the NPC leading to the development of microcephaly. (12) On examination of the fingerprint, it was found that several proteins like Pre-MRNA Processing Factor 8 (PRPF8) and Splicing Factor Proline and Glutamine Rich (SFPQ), and pathways such as RNA processing, were affected by the infection, causing brain growth impairments. (12) Specifically, the ZIKV infection caused downregulation of the RNA processing pathway but increased DEAD Box Helicase 6 (DDX6), which is a critical part of the pathway responsible for mRNA degradation. Furthermore, the splicing factor PRPF8 is upregulated and SFPQ is downregulated by ZIKV which in turn causes the dysregulation of RNA translation and affects NPC proliferation as required for neuronal migration and differentiation. (13) Additionally, there is an upregulation in the CDKN1A gene, which is responsible for cell cycle arrest, relating to the theory that ZIKV infects and causes the death of NPC which induces microcephaly. Where most of these factors have an indirect link to the theory that the inhibition of the Akt-mTOR pathway leads to microcephaly, a direct correlation was found between the increase in DDX6 and the downregulation of the Akt-mTOR pathway. This strengthens the theory that ZIKV-induced inhibition of this pathway may be the mechanism driving microcephaly. (14)

As a collection examination, there was a difference in the incubation of the ZIKV to NPC which may have caused the disparity in presentation and overall analysis.

B. Disruption of vascular structure

An alternative theory suggests that ZIKV molecules interrupt the placental and blood brain barrier (BBB), causing leakage of immune cells into the neurosphere and inducing microcephaly. Post-infection analysis of foetal brains indicated a significant increase in vessel density and diameter of the cerebral cortex, evidence of a leaky BBB. (15) Another study found that the virus can infect human placental trophoblast cells and reduce the ZO-1 and occludin between the cells, which are adhesion proteins critical for maintaining cellular integrity. (16) On the contrary, the results suggested that the ZIKV may cross the placenta barrier by changing the permeability of the barrier cells. However, ZIKV crosses the BBB barrier cells through transcytosis, not changing the permeability. There is evidence that discredits the theory of ZIKV not changing the permeability of the BBB, stating how ZIKV crosses the monolayer of BBB barrier cells in the presence of the treatment of endocytic inhibitors. This suggests that we still cannot exclude the possibility that some viral particles selectively modulate tight junctions and cross the BBB. The reliability of the results also came into question when the study did not analyse some infected cells due to them being infected with multiple strains of ZIKV. Nonetheless, the evidence suggests that the compromised vascular integrity likely impairs neural proliferation, contributing to microcephaly. (16)

Another study took a different approach and studied how the infection of astrocytes, which maintain the BBB, induced CD8+ T cell infiltration, initiating ZIKV–associated paralysis. (17) CD8+ T cells infiltrate into the brain and can limit ZIKV replication within neurons. However, this antiviral process comes at the cost of neuropathogenesis, leading to microcephaly symptoms such as hindlimb paralysis. (18) A study supporting the theory that astrocytes are affected found that ZIKV infection caused mitochondrial overload, increasing reactive oxygen species (ROS). (19) ROS have a direct impact on the permeability of astrocytes by compromising cellular and junctional integrity, which can disrupt the supportive roles of astrocytes in brain development. While this mechanism may not be the sole cause of microcephaly, it could be a contributing factor. Notably, while most studies utilized human-derived cells, the investigation of CD8+ T cell infiltration was conducted on LysMCre+Ifnar1fl/fl mice. (18) The authors acknowledged that differences in neuropathology between species could influence the reliability of their results.

C. Dysregulated immune response

Another theory on how ZIKV induces microcephaly is through the dysregulation of the immune system. An analysis of the global transcriptome of the developing mouse brain infected with ZIKV showed there was an upregulation of genes responsible for the immune response and apoptosis pathways. (20) There were some notable changes, where the genes related to cytokine production and the response of cytokines were upregulated. This implies that the cytokines contribute a great deal to the pathogenesis of the ZIKV infection. It was confirmed from this study that the genes including Tlr3, Ifih1 and Oas2, in addition to Ccl5, Cxcl10, and Ifnb1 were expressed in infected brains. (20) Moreover, a similar study on mice concluded that sub-networks involved in neurogenesis and neural development such as the microglial and immune response were dysregulated in the infected brain. They stated how the genes associated with the viral and immune response, specifically cytokine-mediated signalling was most enriched, corroborating the previous study. Although the networks to produce the most cytokines were induced, TNF-α and IL-6 were the most prominent ones in the analysis, followed by various interferons. (21) The expression of nearly 40 genes involved in the c-Jun N-terminal kinases (JNK) pathway was significantly dysregulated in the infected brains. The JNK pathway regulates a range of biological processes implicated in tumorigenesis and neurodegenerative disorders. The downregulation of this pathway can reduce the proliferation of neural progenitor cells and increase cell death, leading to defective tissue growth. In addition, many of the significantly induced genes engaged in cytokine production or response, such as TNF, Il1b, Tlr3, Tlr4 and Tlr6.

It was suggested by another study that the ZIKV infection causes an increase in interferons and cytokines but through the infection and increased expression of microglia, known as the brain's immune cell. (7) Infection of microglial cells resulted in the elevated expression of interferon type I (IFN-α and IFN-β) and type II (IFN-γ) and neurotoxic factors with strong proinflammatory effects such as (TNF-α, IL-1β, IL-6). (22) On the other hand, the extent of the upregulation of the factors was dependent on the strain of ZIKV and the type of infected cell, questioning the reliability of the conclusion. It was also found that infection of microglial cells resulted in the increase of nitrous oxide (NO) production, which is shown to induce NO-mediated neuronal cell death.

CONCLUSION

In conclusion, ZIKV may induce microcephaly by a variety of different mechanisms. The studies conducted on cellular and murine models have shown that ZIKV can induce microcephaly by the infection and degeneration of NPC, disruption of the cerebral vascular system, or dysregulation of the immune system. Despite research showing different theories and contradicting mechanisms, there is no conclusive concept. It is difficult to compare studies due to the variations in the tissue or cells used along with the different strains of ZIKV. While there is an established causal association between ZIKV and microcephaly, a single theory or mechanism cannot be confirmed due to there not being enough studies on human tissues. Considering the ethical limitations of research on foetal tissues, further investigations should focus on establishing whether degeneration of NPC, disruption of the cerebral vascular system, or dysregulation of the immune system are solely responsible for the induction of microcephaly. The mechanism of how this is achieved needs to be studied further, aiding in the development of any sustainable treatment of the ZIKV infection.

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