

Zika Virus, Congenital Infection, and Neurologic Manifestations in Children: A Narrative Review

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Abstract

Context: Zika virus (ZIKV) is an arbovirus of the family *Flaviviridae*. This virus, which is transmitted by mosquitoes, usually affects children and causes self-limited diseases, associated with fever, maculopapular rash, conjunctivitis, arthralgia, and myalgia. There is a significant relationship between ZIKV infection and central nervous system disorders in infants. In this study, we aimed to review neurologic manifestations of ZIKV infection in infants.

Evidence Acquisition: We searched the following Mesh terms in scientific databases: "Zika virus", "infants", "children", "neurologic manifestations", and "congenital infection". Electronic databases including Google Scholar, Science Direct, PubMed, Web of Science, Scientific Information Database, and Scopus were searched from 2000 to 2016.

Results: The literature review showed a probable relationship between ZIKV infection and prevalence of microcephaly in newborns. Besides microcephaly, other central nervous system abnormalities included abnormal gyral arrangement, decreased brain parenchymal volume, cortical atrophy and malformation, cerebellar hypoplasia, and delayed myelination of the brain stem.

Conclusions: Vertical transmission of ZIKV in pregnant women is associated with intrauterine infection and brain malformations in the developing fetus, including microcephaly, calcification, cortical displacement, ventriculomegaly, and white-matter abnormalities.

Keywords: Zika Virus, Clinical, Neurologic Manifestation, Congenital Infection

1. Context

Zika virus (ZIKV) is an arthropod-borne virus (arbovirus) of the family *Flaviviridae* and category *Flavivirus*, transmitted by mosquitoes of the genus *Aedes* (1). Clinical manifestations of ZIKV infection resemble diseases caused by other viruses, including dengue fever and chikungunya. These patients normally have an asymptomatic infection or a mild, self-limited, febrile disease (2).

The most common symptoms of ZIKV infection include rash, fever, nonpurulent conjunctivitis, and arthralgia (3). In addition, neurological findings include congenital microcephaly and other developmental complications, such as Guillain-Barre syndrome (GBS), myelitis, and meningoencephalitis, among children born to women with infection during pregnancy (4-8). On November 24, 2015, the healthcare system of French Polynesia described a strange increase in fetal and neonatal central nervous system (CNS) abnormalities (9). CNS malformations in infants had occurred through mother-to-child transmission (transplacentally or during delivery) (10).

2. Evidence Acquisition

The literature review was performed using the following Mesh terms: "Zika virus", "infants", "children", and "neurologic manifestations". The search was carried out in different electronic databases, including Google Scholar, Science Direct, PubMed, Web of Science, Scientific Information Database, and Scopus during 2000 - 2016.

3. Results

3.1. Epidemiology

From 1947 to 2007, ZIKV was reported as only a sporadic human infection (< 20 cases) in some tropical regions of Africa and Southeast Asia (11-13); based on the reports, over 70% of the infected patients were ≥ 3 years (13). In the winter of 2013 - 2014, a widespread outbreak was reported in the French Polynesian islands, affecting approximately 1% of the general population (14). During 2014 - 2016, an epidemic occurred in New Caledonia (nearly 1500 cases) and Martinique island (> 150 cases) (15, 16).

At present, there is a ZIKV epidemic in America, the Caribbean islands, and Asia-Pacific regions. According to

the world health organization (WHO), ZIKV is spreading quickly (17, 18). For the first time, ZIKV was isolated from *Aedes africanus* in 1948 and then from other mosquitoes, belonging to the *Aedes* genus (ie, *Aedes furcifer*, *Aedes luteocephalus*, *Aedes vittatus*, *Aedes apicoargenteus*, and *Aedes aegypti*) (19, 20).

The main route of ZIKV transmission is mosquito bite during blood nourishing. However, there are other routes of transmission, including prenatal and perinatal routes (through the placenta or during delivery), as well as the saliva. The virus may be also transmitted during sexual activities (10, 21, 22). Recently, a probable relationship between intrauterine (congenital) ZIKV infection and microcephaly was reported among newborns in Brazil in October 2015 (23). Also, about 150 to 200 neonates were born with microcephaly in Brazil during 2010 - 2014 (24).

On November 17, 2015, the healthcare system of Brazil reported ZIKV RNA in amniotic fluid specimens from 2 pregnant women with fetal microcephaly, confirmed by reverse transcription-polymerase chain reaction (RT-PCR) assay (24). These women had manifestations compatible with ZIKV infection at the gestational age of 18 and 19 weeks, respectively. Moreover, in November 2013, the first perinatal transmission of ZIKV was reported in French Polynesia. The neonate had a maculopapular rash at birth, and the mother described a disease compatible with ZIKV infection at 2 weeks before delivery (10).

3.2. Clinical Features

3.2.1. Infection and Disease in Healthy Subjects

Nearly 80% of ZIKV-infected individuals remain asymptomatic. This group of patients is regarded as a main source of infection transmission to others (11). The incubation period of ZIKV is 2 - 14 days, similar to other mosquito-borne *Flavivirus* infections (25). The majority of children, who are infected with ZIKV through mosquito bites, remain asymptomatic or have a mild disease, similar to ZIKV-infected adults (26). These children become infected through 3 routes: vertical transmission during pregnancy (intrauterine), transmission in the perinatal period (intrapartum), and mosquito bites (postpartum infection) (26).

In 2007, the most common signs and symptoms of ZIKV infection in Yap Island, Micronesia were fever, macular or papular rash, arthralgia, and conjunctivitis among people within the age range of 1 - 76 years. The age group of 0 - 19 years reported fewer attacks in comparison with adults aged 20 - 59 years (13). Also, in Africa, Asia, South America, and Pacific regions, fever without rash was reported among children with ZIKV, aged 3 - 16 years. Other associated symptoms included conjunctivitis, arthralgia, vomiting, and diarrhea (27, 28).

Among cases reported in the United States, all infants (n = 8) had rashes, along with other symptoms including fever, arthralgia, and nonpurulent conjunctivitis (29). Infants and young children may demonstrate irritability, walking abnormalities, bodily pain, and pain on palpation; also, pain with active or passive movements of the affected joint has been reported (13). However, developmental problems, caused by ZIKV infection, have not been detected in otherwise healthy infants with postnatal infection (30, 31).

Overall, death due to ZIKV infection seems to be rare among otherwise healthy individuals with postnatal infection and is infrequent in all age groups. However, the literature search indicated 2 cases of death in a 15-year-old girl with sickle-cell anemia and a 16-year-old female with signs such as headache, nausea, and petechiae. In general, clinical symptoms of ZIKV infection include headache, fever, chills, pharyngitis, lymphadenopathy, maculopapular rash, joint and muscle pain, and nonpurulent conjunctivitis (13-32).

Moreover, gastrointestinal problems including nausea, vomiting, diarrhea, constipation, abdominal discomfort, and aphthous ulcers have been detected in infected patients (28). Other signs in these patients are leucopenia, neutropenia, lymphopenia or lymphocyte activation, monocytosis, thrombocytopenia, and elevated serum levels of lactate dehydrogenase, aspartate aminotransferase, glutamyl transferase, fibrinogen, ferritin, C-reactive protein, and erythrocyte sedimentation rate in the period of viremia (15, 33-36).

Chronic fatigue syndrome has been also reported following infection with ZIKV (37, 38). In addition, idiopathic thrombocytopenic purpura and cardiac diseases have been recorded in some studies (39). ZIKV infection is commonly self-limiting, and the clinical signs resolve almost completely within 3 to 7 days (11, 40). Overall, ZIKV infection should be considered in people younger than 18 years, who have traveled to or stayed in an infected region within the past 2 weeks and have 2 or more of the following manifestations: fever, rash, conjunctivitis, and arthralgia (26).

3.2.2. Intrauterine and Congenital Infection

For the first time, the relationship between ZIKV infection and microcephaly was reported in October 2015 in Northeastern Brazil (41). On November 28, 2015, the health system of Brazil reported the presence of ZIKV genome in the blood and brain tissue samples of an infant with microcephaly (42). In such cases, the virus is transmitted during pregnancy and infects the fetal brain, where it targets and destroys neural progenitor cells and neuronal cells at all stages of maturity. In the fetal brain, ZIKV infects neurons

and glia cells and impairs normal brain development. In addition, neuronal growth, proliferation, migration, and differentiation are disrupted (43-45).

There is a risk of vertical transmission throughout pregnancy, especially during the first or second trimester (23, 46). Following the ZIKV epidemics in Brazil, a 20-fold increase was reported in the annual prevalence of microcephaly (47). The reports indicated that all mothers of infants with severe microcephaly had lived in or traveled to ZIKV-infected places during their pregnancy (23).

The most common CNS abnormalities of the fetus are ventriculomegaly, microcephaly, and intracranial calcification, especially at the gray-white matter junction (48, 49). The prevalence of microcephaly due to ZIKV infection in the first trimester of pregnancy ranges from 0.88% to 13.2% (50). According to WHO reports, ZIKV-related microcephaly occurs if the mother has ZIKV infection during pregnancy and the amniotic fluid test can detect ZIKV in PCR (51). Approximately 4000 cases of microcephaly were recorded in Brazil between mid-2015 and January 2016, compared with 163 cases reported annually between 2010 and 2014 (23, 52).

Furthermore, ZIKV can lead to fetal death and ocular abnormalities, such as macular atrophy and loss of foveal reflex in infants with microcephaly (53-57). Imaging findings of patients have revealed intracranial calcifications in the parenchyma, thalamus, and periventricular regions, resembling other congenital infections (eg, cytomegalovirus infection and toxoplasmosis).

Vision-threatening ocular symptoms include segmental pigmentation of the retina, chorioretinal and optic nerve atrophy, enlargement of optic disc cupping, hemorrhagic retinopathy, and abnormal retinal vasculature in children with microcephaly (58-60). Other signs in these patients include clubfoot and contracture of solitary or several joints (arthrogryposis), resulting in CNS impairment (61).

3.2.3. Neurologic Manifestations

A variety of neurological disorders, associated with microcephaly, have been reported in children with confirmed congenital ZIKV infection (61, 62). Also, GBS has been described following ZIKV infection. This syndrome may occur among older patients (63); however, it is unclear how often it occurs in infants following ZIKV infection (64). In French Polynesia, among 38 confirmed cases of GBS due to ZIKV infection, none were infants (65). However, a previous study from Brazil reported 6 patients, aged 2 - 57 years (66).

Besides microcephaly, other CNS abnormalities associated with ZIKV infection include: 1) presence of extraaxial fluid; 2) abnormal gyral arrangement (polymicrogyria); 3) decreased brain parenchymal volume; 4) cortical atrophy

and malformation; 5) hypoplasia of the cerebellum, vermis, or brain stem; 6) delayed myelination; and 7) thinning or hypoplasia of the corpus callosum (49, 54-56, 67). Neurologic examination of ZIKV-infected children has demonstrated hypertonia, hypotonia, spasticity, hyperreflexia, severe irritability, and seizure (61, 62). Critical ZIKV infection should be considered in newborns in the first 2 weeks of life in case the mother has been to an infected place within 2 weeks before delivery (26).

3.3. Diagnosis

ZIKV laboratory tests should be considered in pregnant women who travel to regions with active ZIKV, as well as neonates born to these women (68, 69). These laboratory tests include RT-PCR for symptomatic patients or those with exposure to the virus within the past 2 weeks and serological assessment for people, exposed to the infection within the past 2 to 12 weeks. However, false-positive test results could be detected in patients infected with other flaviviruses; in fact, a negative test result does not ultimately reject ZIKV infection (70).

A specific test of ZIKV is the plaque reduction neutralization test, which measures virus-specific neutralizing antibodies (anti-ZIKV IgM antibodies) (71). ZIKV RT-PCR test should be performed on both infant's serum and urine samples. Also, ZIKV Detect™ IgM ELISA should be simultaneously performed on the serum within the first 2 days of life. In general, laboratory tests for pregnant women with ZIKV infection include RT-PCR to detect ZIKV RNA in maternal samples and positive Zika virus IgM with confirmatory neutralizing antibody titer for ZIKV or flaviviruses.

RT-PCR assay and Zika virus IgM test in the cerebrospinal fluid are not performed unless the cerebrospinal fluid is obtained from other assessments (72). A positive RT-PCR of serum or urine samples approves congenital ZIKV infection. Also, positive Zika virus IgM test results, along with negative RT-PCR findings, demonstrate probable congenital ZIKV infection (72).

Children with positive results for congenital ZIKV infection should undergo ophthalmologic and hearing (by auditory brainstem response test [ABR]) examinations before the first month of birth (71). If hearing screening shows normal results, ABR should be performed at the age of 4-6 months (71). All infants with congenital ZIKV infection should be investigated in terms of neurodevelopment, vision, hearing, feeding, growth, and endocrine function in the first year of life (71).

In the autopsy of fetuses with microcephaly, complete agyria, hydrocephalus, and multifocal dystrophic calcification in the cortex and subcortical white matter were reported, along with cortical disarticulation and mild focal inflammation; ZIKV originated from the fetal brain tissues

on RT-PCR assay (73). Based on previous reports, children with acute ZIKV infection (onset of symptoms within the past 7 days) should be assessed by RT-PCR assay. If ZIKV RNA is not distinguished and the signs are present for more than 4 days, the serum can be used for Zika virus IgM (and neutralizing antibodies), as well as Dengue virus IgM (and neutralizing antibodies) (26).

Laboratory assessment of ZIKV infection in infants includes evaluation of ZIKV in culture, ZIKV RNA or antigen, and positive IgM for ZIKV with verified neutralizing antibody titers 4 times (or more) higher than Dengue virus neutralizing antibody titers (69). ZIKV RT-PCR positivity on amniotic fluid is a diagnostic criterion for fetal viral exposure, although it is not predictive of the outcomes. ZIKV RT-PCR test of amniotic fluid may remain sensitive and specific for more than 21 weeks, depending on the time of amniocentesis after the onset of maternal infection (10).

3.4. Prevention and Treatment

The most effective way to prevent ZIKV infection is personal protection against mosquito bites by using air-conditioned rooms during sleep and permethrin-treated clothes and gear. Also, pregnant women should not travel to places with ZIKV infection. In fact, mosquito-repellent measures should be taken if traveling to regions with ZIKV epidemics. There is no vaccine for the prevention of ZIKV disease yet, although a vaccine is under development (74-78). Also, there is no specific treatment for infected patients or fetuses.

4. Conclusions

ZIKV is an arbovirus, which is transmitted by mosquito bites. Disease in otherwise healthy people is mild and includes fever, arthralgia, and skin rash. Vertical transmission of ZIKV in pregnant women is linked with intrauterine infection and brain malformations in the developing fetus, including microcephaly, calcification, and other developmental abnormalities. There is no specific treatment for ZIKV infection. However, the best method to prevent infection is to avoid exposure to mosquito bites, using different preventive methods. Also, attention should be paid to women who travel to places with a recent ZIKV epidemic during pregnancy.

Footnotes

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