Ophthalmologic Manifestations Associated With Zika Virus Infection

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abstract

Vision plays an important role in the development of communication, social interaction, spatial awareness, and the motor skills needed to explore the environment. In the past 2 years, researchers have described the broad spectrum of clinical features that comprise congenital Zika syndrome (CZS). The ocular manifestations are considered 1 important pillar of this new entity. The most characteristic ophthalmic findings include chorioretinal scars and focal pigmentary changes seen in the macular region. Since these findings were first reported, other researchers have validated and extended them, leading to a more complete picture of the spectrum of ocular manifestations related to CZS. In this article, we summarize the current knowledge on the ocular implications of CZS and emphasize the importance of early rehabilitation to enhance visual performance in affected children.

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Although the Zika virus (ZIKV) was first detected in Brazil 2 years ago, ongoing repercussions of the epidemic are still being felt worldwide. Considered endemic in Africa and Asia for >60 years, this *Flavivirus* had not been associated with birth defects before October 2015.[1,2] After more microcephaly cases were reported in northeastern Brazil, researchers in several studies showed the virus's capacity to attack neural progenitor cells, causing microcephaly.[3–7]

In addition to the dramatic neurologic alterations seen in these Brazilian infants, ZIKV may cause other systemic findings and malformations. Researchers in the latest review conducted by the Centers for Disease Control and Prevention (CDC) concluded that the distinct features of this novel entity, named congenital Zika syndrome (CZS), include severe microcephaly with partially collapsed skull; brain abnormalities, including thin cerebral cortices and subcortical calcifications; macular scarring and focal pigmentary retinal mottling; congenital contractures, including arthrogryposis and clubfoot; marked early hypertonia and symptoms of extrapyramidal involvement; and hearing loss.[8] Although Brazil was the first country to report cases of CZS, the last update from the World Health Organization stated that 29 countries and/or territories have reported microcephaly and other central nervous system (CNS) malformations that are potentially associated with ZIKV infection or suggestive of CZS.[9]

OCULAR FINDINGS IN CZS

So far, studies have revealed that between 21.4% and 55.0% of infants with CZS present with structural ocular findings.[10–13] Despite researchers in most studies showing that ZIKV damages essentially the posterior segment of the eye, including the retina, optic nerve, and retinal vessels, other publications describe additional findings, such as iris coloboma, lens subluxation, cataracts, glaucoma, and microphthalmia.[10,11,14–19] Oculomotor findings have also been described in the literature, including strabismus and nystagmus, which are probably due to the important neurologic and ocular abnormalities that these children may present with.[11,12]

Although CZS can present with a broad spectrum of ocular findings, the most distinctive are the pigment mottling and chorioretinal atrophy that are commonly seen in the macular region.[10,11,14,15] These ocular findings were first described after being identified in infants from the state of Pernambuco, which is located in northeastern Brazil, and were later supported by other publications from other states in Brazil, including Bahia, Ceará, and Rio de Janeiro.[10–14] More recently, Yepez et al[20] reported similar ocular manifestations in affected infants from Colombia and Venezuela, which reinforces the consistency of these findings and the importance of ocular screening in newborns with a high suspicion for CZS.

For a better understanding of these ocular abnormalities, Ventura et al[21,22] have conducted other relevant studies. In 1 of them, they analyzed the main risk factors associated with the ocular findings seen in children with CZS, which revealed that infants whose mothers reported symptoms during the first trimester of pregnancy and in those who were born with more severe microcephaly have a higher chance of presenting with ocular findings.[21]

There is another interesting study in which Ventura et al[22] analyzed the affected retinal tissue in infants with chorioretinal scars caused by ZIKV by using optical coherence tomography (OCT). This was the first study performed in infants' eyes in which the affected layers in the retina were shown. The OCT images revealed a discontinuation of the ellipsoid zone and hyperreflectivity underlying the retinal pigment epithelium, retinal thinning, choroidal thinning, and a colobomatouslike appearance. In addition, in subsequent reports, de Oliveira Dias et al[23] and Campos et al[24] described similar OCT findings in infants with CZS that corroborated the initial OCT study. The importance of these 2 studies is that they indicated how severely ZIKV affects the fetal eye, causing severe and irreversible retinal and choroidal damage. These severe OCT findings made us postulate severe visual impairment in these cases. However, until recently, no researchers addressed visual impairment in infants with CZS.

In a recent study, Ventura et al[25] addressed this research gap. To evaluate visual impairment in children with CZS, the study was designed by using tools to test visual acuity, visual function, and visual developmental milestones. A total of 32 infants with CZS were examined, and Ventura et al[25] concluded that regardless of structural ocular manifestations, all the children with CZS presented with visual impairment. These new data are reminiscent of cortical or cerebral visual impairment (CVI), a term that is used to describe visual impairment related to brain damage and usually affects the visual processing centers and visual pathways of the brain.[26,27] In general, children with CVI encompass a wide range of visual disabilities, from no light reception to normal visual acuity with cognitive visual dysfunction.[27,28] In a similar manner, children with CZS are at an increased risk of presenting with visual disabilities because of the neurologic and neuroimaging findings that are usually present, including microcephaly, cerebral cortex malformation, calcifications, abnormal brain development, and severe neurologic impairment.[29,30]

This statement is supported by several mice-model studies that revealed that ZIKV severely attacks human neural progenitor cells, causing cell death and restricting neurodevelopment.[3–7] More precisely, van den Pol et al[6] identified ZIKV infection in the retinal tissue of mice as well as in the CNS visual system, which reinforces our postulate that brain damage is the main etiology of a child's visual impairment in CZS.

PATHOPHYSIOLOGY OF OCULAR FINDINGS

No researchers had addressed the pathophysiology of the ocular findings in CZS until recently, when van den Pol et al[6] and Singh et al[7] conducted independent mice-model experiments addressing this matter. van den Pol et al[6] focused on examining the brain, CNS visual system, and retina and identified damage caused by ZIKV throughout the entire visual system, including the retina, optic chiasm, suprachiasmatic nucleus, lateral geniculate nucleus, and/or superior colliculus. Thus, in this study, they postulated that ZIKV spreads to other parts of the brain by axonal transportation and that the glial cells are key to understanding the mechanism behind the neurologic and ocular findings.[6]

Interestingly, Singh et al[7] conducted a different study in which they focused solely on the pathophysiology of the retinal findings identified in CZS. In their study, Singh et al[7] provided evidence that the retinal pigmented epithelium is highly permissive and susceptible to ZIKV-induced cell death and concluded that the retinal lesions in CZS occur because of the virus's capacity to break the blood-retinal barrier. Thus, the researchers in these 2 initial studies suggested that the ocular findings in CZS may be caused by different mechanisms: axonal transportation and local damage of the retinal pigmented epithelium.

In a subsequent murine-model study, Zhao et al[31] showed that ZIKV affected multiple layers of the retina. However, the primary target was the Müller glial cells, which displayed decreased neurotrophic function and increased proinflammatory cytokines after infection.

To corroborate Zhao et al's[31] findings, in a most recent study, Aleman et al[32] provided the first in vivo evidence in humans showing a thinning of the ganglion cell layer, which suggests an in utero depletion of this neuronal population as a consequence of ZIKV infection.

OCULAR FINDINGS IN CZS WITH NORMAL HEAD CIRCUMFERENCE AT BIRTH

In the beginning, microcephaly was the birth defect that caught the attention of family members, physicians, and society. As these children began receiving comprehensive assessments, physicians noticed that microcephaly was only the tip of the iceberg, and other abnormalities could be present, including the ocular findings.[2,8] However, because microcephaly was easily identified and considered the main finding in these children, for months, it persisted as a required criterion for further ZIKV investigation.

This criterion only became obsolete when investigators started reporting cases in infants with normal head circumference at birth who presented with other neurologic and ocular findings. The first 2 case patients reported by Ventura et al[33] and van der Linden et al[34] were both from the state of Pernambuco in Brazil. Furthermore, the first travel-related CZS case patient from the United States presented with similar clinical findings, corroborating the new idea that microcephaly is not a required criterion for CZS screening.[35]

SCREENING FOR OCULAR FINDINGS IN NEWBORNS

The current CDC guidelines recommend an initial clinical evaluation comprising a comprehensive physical, neurologic, hearing, and ophthalmologic examination for (1) infants born to mothers with laboratory evidence of ZIKV infection during pregnancy and (2) infants who have abnormal clinical or neuroimaging findings that are suggestive of CZS and have a maternal epidemiologic link suggesting possible transmission regardless of maternal ZIKV test results.[36] Nevertheless, a recent study by Zin et al[13] revealed that eye abnormalities may be the only initial finding in CZS and suggested that all infants with potential exposure to ZIKV in utero should undergo eye screening regardless of CNS abnormalities.

The ocular examination should be performed before hospital discharge or within 1 month and include anterior segment and fundus evaluation. It is important to emphasize the importance of performing a thorough fundus examination with adequate pupil dilation because retinal findings can be discrete and almost imperceptible. In addition, the CDC recommends repeating the ophthalmologic evaluation at 3 months of age for those infants with a confirmed diagnosis.[36]

DIAGNOSING ZIKV INFECTION

The most common symptoms reported in acquired Zika infection (AZI) are maculopapular rash, arthritis or arthralgia, and nonpurulent conjunctivitis, which are nonspecific symptoms, making it difficult to diagnose patients clinically. Moreover, these symptoms are present in only 20% of infected patients.[37] Thus, physicians really need laboratory testing to confirm ZIKV infection. The tests that are

available include molecular tests to identify the presence of ZIKV RNA by using polymerase chain reaction technology, serology (immunoglobulin M [IgM]), and plaque-reduction neutralization tests for equivocal cases.[38]

The purpose of performing a polymerase chain reaction is to detect a live virus, which confirms ZIKV infection, and no further testing is needed. Despite being the most accurate test, it can be used only during the acute viremia phase.

After the acute phase of infection, serologic tests using ZIKV-specific IgM and neutralizing antibodies are used for diagnosis. Unfortunately, the currently available IgM test can be difficult to interpret secondary to nonspecific reactivity and cross-reactivity to other *Flaviviruses*; therefore, a positive result must be followed up by a confirmatory plaque-reduction neutralization test.[38]

TREATMENT

Although scientists have been investing immense effort in developing an effective vaccine and antiviral agents to prevent new CZS cases, these measures are still not available and will not revert the existing cases.[39–43]

Children with CZS present with severe and multiple disabilities, which require constant care and a variety of therapies. The clinical and rehabilitation treatment must be personalized for each patient and address each of their necessities. The best way to assist patients with CZS is to provide multidisciplinary care involving trained physicians and therapists. As part of this team, ophthalmologists play an important role. They are part of the frontline of care and are responsible for detecting ocular lesions and initiating early intervention for visual development in infants with CZS.

The reason children with CZS need ocular and visual screening early in life is to detect potential visual impairment associated with the ocular findings and/or CVI to provide interventions during the critical period of neuroplasticity.[44] This period provides a window of opportunity for neuronal activity that is responsible for vision to be routed from the damaged areas of the visual pathways and primary visual cortex to other areas of the brain that are responsible for visual function.[44]

The assessment of children with CZS requires a multidisciplinary team and includes a comprehensive ophthalmic examination, an assessment of visual function and visual milestones (performed by ophthalmologists), and a functional vision assessment (performed by therapists).[25,44] Identifying and treating infants who present with known causes of visual impairment, including refractive errors, anisometropia, hypoaccommodation, amblyopia, and strabismus, are key. In addition, regardless of ocular findings, many of these children may need magnifying glasses, patching, visual stimulation therapy to promote visual development and potentiate their remaining vision, and (in selected cases) strabismus surgery.[25]

Of note, the capacity to make use of residual vision also depends on a child's ability to neurologically process and understand environmental sensory information.[45] Thus, treatment needs to be customized to maximize the child's residual vision by considering the complex interaction of the visual process, CNS functioning, and environmental stimuli.[46,47]

OCULAR FINDINGS IN AZI

The main difference between the ocular findings seen in AZI and those identified in CZS is the presence of active uveitis, which has been reported only in AZI. Interestingly, adults who have presented with ocular manifestations during viremia (regardless of the treatment) had complete regression and recovery of their vision after the viremia period and topical treatment with steroids, and, in some cases, hypertension drops. The main ocular findings reported in AZI include conjunctivitis, hypertensive iridocyclitis, unilateral acute maculopathy, and bilateral posterior uveitis.[48–51]

The first reports of acute uveitis secondary to AZI were reported by Furtado et al[48] and Fontes,[49] who described 2 independent cases of anterior bilateral hypertensive uveitis. Subsequently, Parke et al[50] published a case of unilateral posterior uveitis that resolved within 6 weeks. However, Kodati et al[51] described the most recent and intriguing case. In this case report, a male patient presented with posterior uveitis that persisted with chorioretinal scars despite his visual function resolving after the acute illness. Interestingly, this is the first report in which researchers describe chorioretinal scars in AZI.

CONCLUSIONS

A diversity of ocular findings has been described in adults related to AZI and in newborns related to the vertical transmission of the virus. Undoubtedly, CZS is a challenging disease for families, health care professionals, and public health systems mostly because of the considerable amount of uncertainties involved. Although the life expectancy of children with CZS is questionable, it is important to keep in mind that most infants who were born during the Brazilian outbreak remain alive. Thus, early assessment and intervention are our best bet to diminish the impact on these children and families and to ensure a better quality of life.

ABBREVIATIONS

AZI: acquired Zika infection
CDC: Centers for Disease Control and Prevention
CNS: central nervous system
CVI: cerebral visual impairment
CZS: congenital Zika syndrome
IgM: immunoglobulin M
OCT: optical coherence tomography
ZIKV: Zika virus

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