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Review Article

Neurological Complications of Congenital Zika Virus Infection

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ABSTRACT

BACKGROUND: *In utero* Zika virus infection resulted in many newborns with congenital defects; this public health issue was followed by unprecedented scientific productivity in this field. Many questions remain about congenital Zika virus infection and its maternal transmission, pathogenesis, clinical events, and the resulting neurological damage. There are few review articles that synthesize the current knowledge of congenital neurological complications as well as the gaps in the pediatric literature.
OBJECTIVE: We review the full range of data on neurological complications in the newborns and infants born to Zika virus-infected women.
METHODS: A research question (PCC: Population, newborns and infants of infected mothers; Concept, neurological outcomes at birth; Context, congenital Zika virus infection) was created to guide our review in searching several databases: PubMed, Lilacs, CINAHL, Cochrane Library, and OpenGrey literature. A total of 34 articles were included in the final review.
RESULTS: Central nervous system calcifications, mainly at the cortical-subcortical junction, were the most prevalent neurological birth defects related to Zika infection (104/112, 92.9% from seven studies). Also, microcephaly occurred in 39.7% of all infected infants (1561/3931 patients in all the studies) and ventriculomegaly and/or hydrocephalus occurred in 63.1% (157/249 patients analyzed in 12 studies). A total of 10 articles detailed ocular findings, including macular lesions, focal pigment mottling of the retina, chorioretinal atrophy, optic nerve abnormalities, cataract, microphthalmia, and strabismus, among others.
CONCLUSIONS: Neurological and related malformations are common lesions in individuals with congenital Zika syndrome. Long-term follow-up studies in this field are lacking.

Introduction

Zika virus (ZIKV) infection is responsible for microcephaly and other severe neurological and fetal malformations in newborns of infected mothers. The 2014 cluster of microcephalic infants in northeastern Brazil surprised local, national, and global authorities. Subsequently, according to the World Health Organization (WHO), ZIKV infection was quickly recognized in more

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than 48 countries, and in 23 countries as a cause of congenital infection, resulting in 757,703 cases of congenital Zika syndrome (CZS) in the Americas.[1] Colombia has the second highest number of fetal ZIKV infections after Brazil.[2] ZIKV was first reported in Colombia in September 2015,[3] and just between 2016 and 2017, a total of 1415 cases of microcephaly and other central nervous system (CNS) disorders were reported in Colombia. Of the 1415 cases, 196 were confirmed at the laboratory, 447 were discarded, 213 did not correspond to microcephaly or other CNS defects, and 559 remained under investigation. Based on modeled estimates, ZIKV infection during pregnancy in Colombia caused three- to fourfold more babies with congenital microcephaly than usual in the period between 2015 and 2017.[4] CZS is characterized by severe microcephaly and other neurological lesions, ocular findings, and congenital contractures. CZS is also related to other abnormalities and/or fetal malformations, such as craniosynostosis, intrauterine growth restriction, craniofacial malformations, pulmonary hypoplasia, and arthrogryposis.[5-7] In February 2016, the WHO classified ZIKV infection as a "highly probable" cause of fetal neurological abnormalities. Two months later, the Centers for Disease Control declared ZIKV a global threat to public health.[8,9]

Considering the neuropathology of brain damage, Chimelli et al.[10,11] speculated that when ZIKV infection occurs at the end of gestation, the resulting brain damage is mild, in contrast to the severe destruction that occurs if ZIKV is acquired during the first trimester, suggesting that the time of infection during pregnancy is one of the most relevant risk factors for the development of CZS. These authors suggest three patterns of ZIKV-induced CNS lesions based on macroscopic findings. The first is characterized by severe ventriculomegaly secondary to midbrain damage with aqueduct atresia or stenosis. In this instance, the occipital lobe sometimes acquires a cystic appearance because it presents little parenchyma, which can be seen in ultrasound (US) images corresponding to Blake's pouch cyst. The second pattern shows a small brain associated with moderate ventriculomegaly (*ex vacuo*), with the presence of shallow grooves or agyria; this is the pattern most often associated with microcephaly. In these individuals, the aqueduct is patent or even dilated. Also, calcifications are easily detected with the reduction of volume or malformation of important structures, such as the hippocampus, corpus callosum, basal ganglia, thalamus, cerebellum, and brainstem. In the first two patterns, the base of the bridge is reduced in size and flat owing to the lack of downward fibers. The third pattern is observed when the infection occurs later in pregnancy. Macroscopically, the brain is generally well formed, with moderate calcification observed in the deep white matter. Histopathological evidence (based on autopsies of infants with severe brain lesions) shows the following in this third pattern of CZS: disordered cellular migration in the cerebral hemispheres, cerebellum, and brainstem; destructive lesions with nerve cell degeneration; apoptosis; gross calcification; hypoplastic lesions secondary to the absence of descending fibers in brain structures, such as the base of the pons and pyramids; and predominantly mild inflammation of TCD8 lymphocytes.

There is evidence that ZIKV weakens the innate immune responses of host cells, allowing for productive replication and potential spread of the virus. In addition, it is assumed that the virus compromises the placenta and therefore promotes selective attack on the neural progenitor cells. Depletion of neural progenitor cells by ZIKV is associated with restricted brain growth and deregulation of the genes involved in cell death, proliferation, differentiation, and migration.[12] The precise mechanism of cell invasion by ZIKV is currently unknown. Several possible receptors have already been identified, including AXL (which is expressed in both the placenta and fetal brain tissues), but some studies have indicated that there are other receptor-dependent and receptor-independent mechanisms, which may also explain the neurotropism and dissemination of ZIKV.[12]

ZIKV-related neurological damage presents mainly as severe microcephaly, in which the baby's brain has impaired growth during pregnancy, does not develop properly, or is damaged at some point during pregnancy, disrupting proper development. Microcephaly is defined by the WHO as "a reduction in head circumference (HC, also called cephalic perimeter) with the occipitofrontal measure of a newborn at 37 weeks of gestation equal to or less than 31.9 cm for boys and 31.5 cm for girls."[13-15] In addition, there is no currently available specific prevention or treatment for the condition itself, only early multiprofessional stimulation to improve the child's physical and intellectual disabilities. Starting these interventions in the early stages after birth requires prompt diagnosis. CNS damage and microcephaly have serious consequences, such as seizures, developmental delay, intellectual disability, hearing loss, vision problems, and incoordination of swallowing.[16]

The objectives of this review were to map the neurological damage and outcomes related to congenital ZIKV infection and identify gaps in the literature that might provide direction for future research.

Methods

Design

The search strategy and whole review process were based on the Joanna Briggs Institute methodology.[17] A review assessment was used to assess the nature and extent of research activity in neurological complications in congenital ZIKV infection. Afterward, all the research findings and gaps within the literature were summarized. This review consisted of a "five-stage framework": identifying the research question, identifying relevant studies, selecting studies, charting the data, and finally, gathering, summarizing, and reporting the results.[18]

Search strategy

The following bibliographical databases were searched for articles from January 1966 to August 2018: CINAHL, Ovid, PubMed, Scopus, Lilacs, Cochrane Library, OpenGrey, and EMBASE. A research question (PCC: Population, newborns and infants of infected mothers; Concept, neurological outcomes at birth; Context, congenital ZIKV infection) was created to guide our review. Then, a subsequent literature search was conducted, using the list of keywords and synonyms described in Fig 1, with the evaluation of the most frequent terms in the literature related to ZIKV infection and microcephaly. Searches for the mesh terms "microcephaly," "Zika virus," "newborn," "congenital infection," and "nervous system malformations" were performed using two or more words close to each other and

((zika OR zika virus [mh]) AND (Child [mh] OR Child* OR Pediatric OR Paediatric OR Child, preschool [mh] OR newborn OR infant, newborn [mh] OR fetus OR fetuses OR fetus [mh]) NOT (zika [Author]))

Figure 1. Example combination of keywords and entry terms for the database searches (PubMed).

synonyms, mesh items, and related terms, including without restriction. The complete final search strategy is detailed in Fig 1.

Titles and abstracts from the literature search were compiled and revised for eligibility for full-text evaluation by two distinct reviewers (V.d.M.M. and P.S.C.). The inclusion criteria for evaluation were (1) patients were newborns or infants and (2) patients had CNS abnormalities related to congenital ZIKV infection (microcephaly and other CNS malformations). Articles were accepted regardless of the original language they were published in. Articles were excluded from this review if they were guidelines, case reports, short comments, interviews, addresses, comments, directories, editorials, guidelines, interviews, or global technical reports. Case reports were excluded to minimize publication bias. Also, studies on other arboviruses, non-Zika congenital infections, or noncongenital infections were excluded (Fig 2).

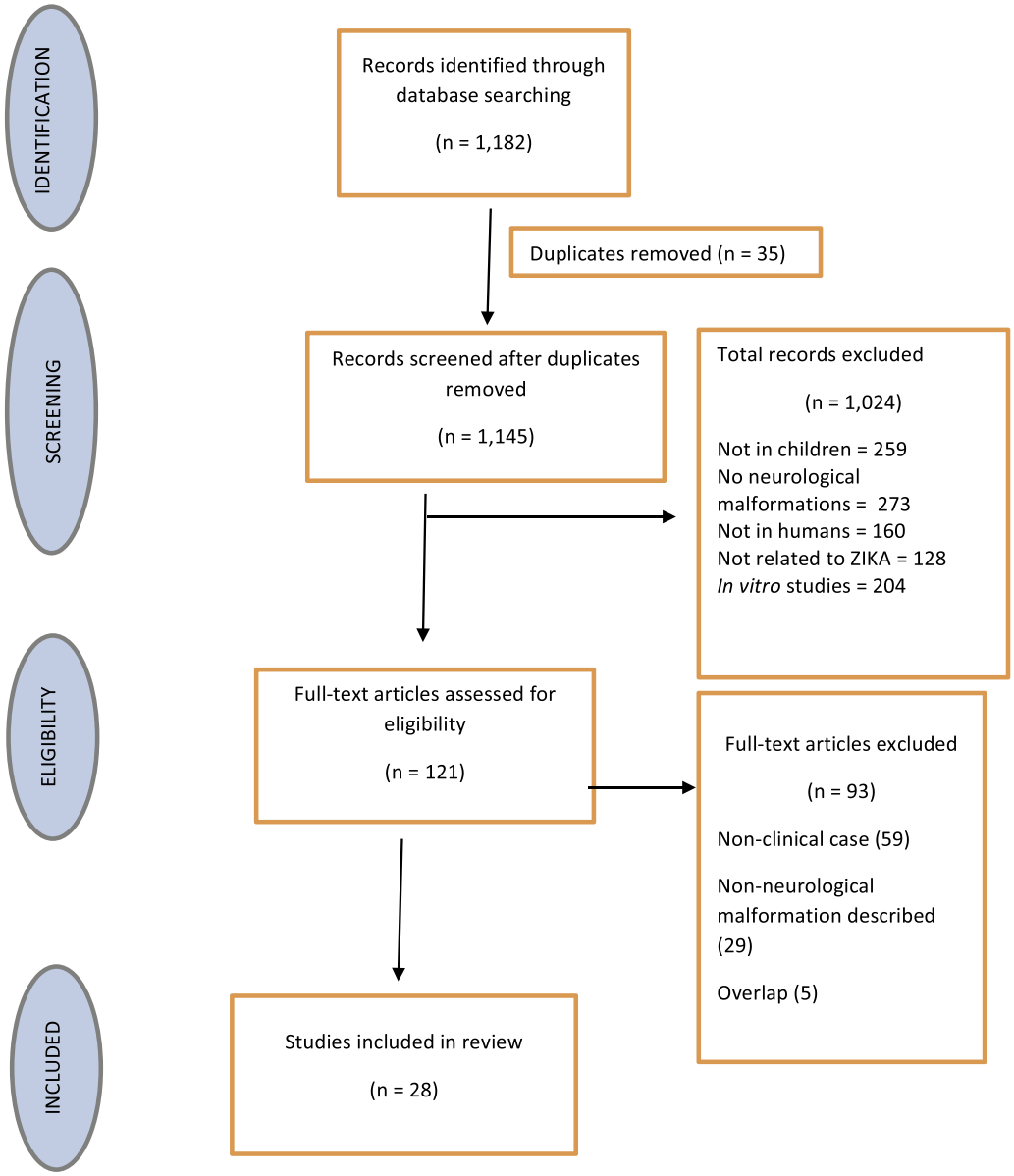

Figure 2. PRISMA flow diagram of neurological complications in congenital Zika virus infection. The color version of this figure is available in the online edition.

Table. Summary of the Characteristics of Articles Reviewed for Neurological Malformations in Congenital Zika Virus Infection

Author (year); Location	Neurological Malformations							
	Microcephaly*	Ventriculomegaly/ Hydrocephalus†	Intracranial Calcifications†				Cerebellar Abnormalities†	Corpus Callosum Abnormalities†
			Total	Subcortical-Cortical Junction	Basal Ganglia	Periventricular		
Brasil et al. (2016); Brazil[19]	4/12 (25.0%)	NA	4/12 (25.0%)	NA	NA	NA	NA	NA
Carvalho et al. (2016); Brazil[20]	29/29 (100.0%)	9/19 (47.4%)	12/19 (63.2%)	NA	NA	NA	8/19 (42.1%)	NA
de Paula Freitas et al. (2016); Brazil[21]	29/29 (100.0%)	NA	NA	NA	NA	NA	NA	NA
França et al. (2016); Brazil[22]	602/1501 (40.1%)	NA	NA	NA	NA	NA	NA	NA
Oliveira et al. (2016); Brazil[23]	574/574 (100.0%)	NA	NA	NA	NA	NA	NA	NA
Sarno et al. (2016); Brazil[24]	52/52 (100.0%)	34/52 65.4(%)	23/52 (44.2%)	NA	NA	NA	NA	2/52 (3.8%)
Schueler-Faccini et al. (2016); Brazil[25]	35/35 (100.0%)	12/27 (44.4%)	20/27 (74.1%)	NA	NA	NA	NA	NA
Soares de Oliveira-Szejnfeld et al. (2016); Brazil[26]	16/17 (94.1%)	16/17 (94.1%)	17/17 (100.0%)	15/17 (88.2%)	11/17 (64.7%)	11/17 (64.7%)	14/17 (82.4%)	16/17 (94.1%)
Van der Linden et al. (2016); Brazil[27]	6/7 (85.7%)	7/7 (100.0%)	7/7 (100.0%)	7/7 (100.0%)	6/7 (85.7%)	5/7 (71.4%)	7/7 (100.0%)	6/7 (81.7%)
van der Linden et al. (2016); Brazil[28]	0/13 (0.0%)	11/13 (84.6%)	13/13 (100.0%)	12/13 (92.3%)	6/13 (46.2%)	0/13 (0.0%)	4/13 (30.8%)	8/10 (80.0%)
Aragão et al. (2017); Brazil[29]	16/19 (84.2%)	10/19 (52.6%)	18/19 (94.7%)	18/19 (94.7%)	4/19 (21.1%)	3/19 (15.8%)	3/19 (15.8%)	11/19 (57.9%)
Honein et al. (2017); USA[30]	22/26 (84.6%)	NA	11/22 (50.0%)	NA	NA	NA	NA	NA
Melo et al. (2017); Brazil[31]	9/11 (81.8%)	7/7 (100.0%)	7/7 (100.0%)	7/7 (100.0%)	6/7 (85.7%)	NA	7/7 (100.0%)	NA
Petribo et al. (2017); Brazil[32]	35/37 (94.6%)	15/37 (40.5%)	37/37 (100.0%)	35/37 (94.6%)	26/37 (70.3%)	4/37 (10.8%)	NA	NA
Pires et al. (2017); Brazil[33]	7/8 (87.5%)	7/7 (100.0%)	7/7 (100.0%)	NA	NA	NA	NA	NA
Cardoso et al. (2018); Brazil[34]	0/19 (0.0%)	NA	NA	NA	NA	NA	NA	NA
Hoen et al. (2018); USA[35]	32/555 (5.8%)	NA	NA	NA	NA	NA	NA	NA
Moreira-Soto et al. (2018); Brazil[36]	26/32 (81.3%)	18/32 (56.3%)	24/32 (75.0%)	NA	NA	NA	NA	NA
Rice et al. (2018); USA[37]	56/943 (5.9%)	NA	NA	NA	NA	NA	NA	NA
Sanz Cortes et al. (2018); Colombia[38]	11/12 (91.7%)	11/12 (91.7%)	11/12 (91.7%)	10/12 (83.3%)	5/12 (41.7%)	8/12 (66.7%)	2/12 (16.7%)	11/12 (91.7%)

* Clinical findings: number of cases/total confirmed ZIKV congenital cases (% of cases)
† Neuroimaging findings: number of findings/total cases that underwent neuroimaging examination (% of cases)

Results

A total of 1182 studies were identified from January 1966 to August 2018. After this step, a final examination was performed to identify any errors or duplications (we removed 35 duplicate records). Most articles (n = 1024) focusing on clinical and radiological CNS malformations were excluded for this review because they were based on animal research, not performed in children, not clinical studies (performed *in vitro*), related to other arboviruses, unrelated to neurological congenital abnormalities, or not related to ZIKV. Then, 121 articles were considered eligible for full-text analysis and 28 were eligible for the final review (Fig 2).

Most of the published studies were conducted in Brazil (80%), followed by the United States (15%) and Colombia (5%); all the studies were published from 2016 (Table). The most prevalent congenital neurological finding associated with ZIKV was calcification (92.9%), mainly at the cortical-subcortical junction, with 104 reported cases of a total of 112 newborns (ranging from 25% to 100% in seven studies). The incidence of microcephaly was 39.7% (1561 of 3931 cases of congenital Zika infection) and reached almost 100% when the infection occurred during the first trimester and decreased when the infection occurred in the second or third trimester. Ventriculomegaly and hydrocephalus occurred in 157 of 249 (63.1%) patients analyzed in 12 studies (the incidence varied from 40.5% to 100% in the individual studies). All neurological data were summarized in Fig 3 and detailed in the Table.

The quality of the studies described in this review was analyzed using the JBI tool (The Joanna Briggs Institute Critical Appraisal tools for use in JBI Systematic Reviews. Checklist for Case Series), and the analysis is available as a supplementary file (Supplemental Figure 1).

Ocular findings were described in detail in 10 studies,[21,24,25,27,31,39-43] with a total sample of 244 infants, resulting in 108 (44.3%) with ocular findings. Bilateral findings were observed in 83 of those with ocular lesions (76.8%). The most frequent findings were macular lesions (pigmentary maculopathy, pigment mottling, lacunar maculopathy, or macular chorioretinal atrophy with and without hyperpigmented borders), optical nerve abnormalities, chorioretinal

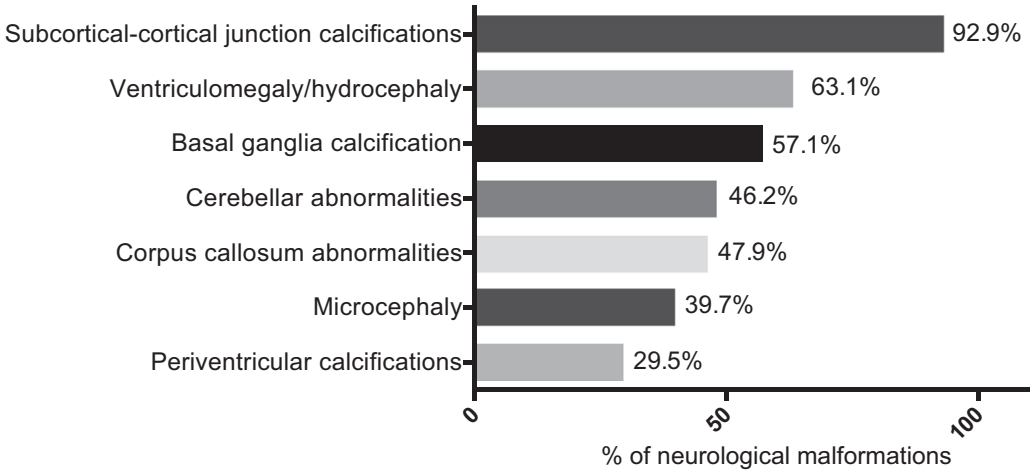

Figure 3. Neurological malformation findings from a total of 3931 infants from 20 clinical and neuroimaging studies.[19-38]

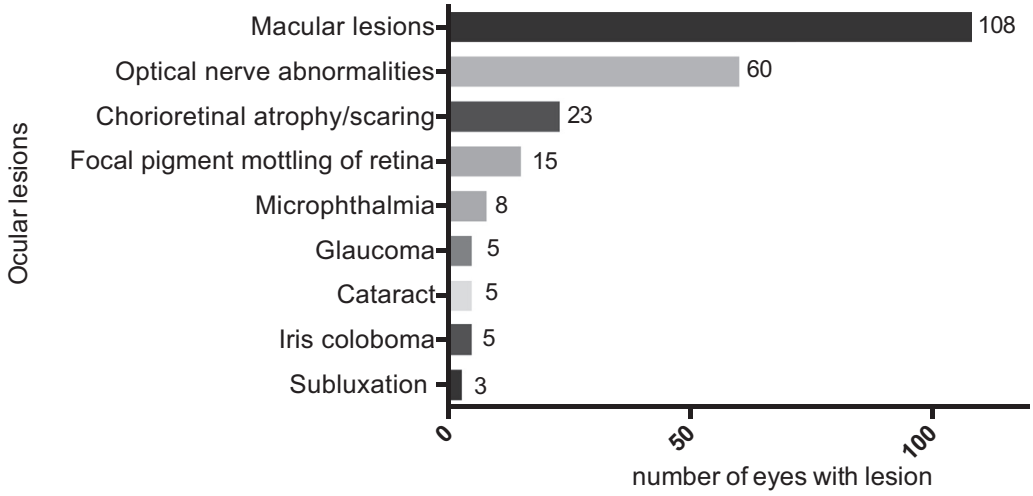

Figure 4. Ocular findings (number of eyes with lesion) from a total of 108 infants with documented ocular lesions.[21,24,25,27,31,39-43]

atrophy/scarring, and focal pigment mottling of the retina, among others (Fig 4).

Finally, a specific search was performed to include aspects related to epilepsy and sleep profiles in congenital ZIKV infection. Van der Linden et al.[44] documented epilepsy in 95 of 141 congenital ZIKV cases (67%), with a mean age of onset of 4.9 months. The seizure types were infantile spasms (72%), focal motor seizures (21%), tonic seizures (4%), tonic-clonic seizures (2%), and myoclonic seizures (1%). Another study that followed 102 children with congenital ZIKV[45] demonstrated that 42.2% developed epilepsy (21.6% infantile spasms, 11.8% generalized, and 8.9% partial); all 22 parents described the spasms as brief jerking spells of flexion and/or extension movements (head, neck, trunk, and members) that lasted a few seconds. One study[46] investigated the sleep characteristics of 88 congenital ZIKV-infected children: 34.1% were defined as poor sleepers and 24% slept less than 9 hours; therefore, sleep disturbances should be investigated in individuals with congenital ZIKV infection.

Discussion

We identified 28 studies with clinical (neurological malformations and epilepsy) and radiological descriptions of CNS malformations related to ZIKV infection. Clinical and radiologic findings support the idea that ZIKV infection in pregnant women has deleterious effects on the development of the fetus, causing abnormalities and birth defects in, mainly, the CNS and ocular system. Also, evidence was documented of ZIKV in fetuses, placentas, newborn tissue, and cerebrospinal fluid with congenital infection, as well as neurotoxicity by ZIKV in the fetal brain, confirming vertical transmission and CZS.[1,47-50]

Although the review conducted in this study sought clinical studies in neonates and human infants, some experimental models deserve discussion. Cugola et al.,[51] using an experimental mouse model, demonstrated the neurotropic characteristic of the Brazilian strain of ZIKV and the delayed neurodevelopment of the mice; additionally, in this study, ZIKV was able to infect *in vitro*

human cortical progenitor cells, resulting in increased rates of apoptosis/necrosis and reduced proliferative zones, with disrupted cortical layers, in neural cell culture systems. Another investigation,[52] using marmosets (*Callithrix jacchus)*, a rat-sized neotropical primate with a hemomonochorial placental architecture that develops early in pregnancy, similar to humans, reinforced the role of the placenta as both a reservoir and conduit of congenital ZIKV infection ("placental pathogenesis").

The neuroimaging patterns of lesions due to ZIKV should be discussed. Some studies described specific neurological damage that was revealed by neuroimaging, including one pictorial essay built by Mehrjardi et al.,[7] who found (1) by US microcephaly, parenchymal atrophy (and secondary ventriculomegaly), subependymal pseudocysts, agenesis/hypoplasia of the corpus callosum, parenchymal calcification (better than magnetic resonance imaging [MRI]), cerebellar and brainstem hypoplasia, and ocular abnormalities and (2) by MRI cortical development (e.g., polymicrogyria), opercular dysplasia, white matter and cortical changes (e.g., abnormal myelination), lissencephaly-pachygyria, and cortical laminar necrosis.[4] Another study also described neurological image findings in congenital ZIKV; all 17 confirmed patients showed parenchymal volume loss and calcifications (mainly at the gray matter-white matter junction). Sixteen of these patients (94%) had ventriculomegaly and showed evidence of cortical abnormalities (lissencephaly, polymicrogyria, pachygyria, or irregular areas of sulci/gyri) as well as corpus callosum abnormalities; additionally, 14 of these patients (82%) had cerebellar abnormalities (hemisphere hypoplasia/maldevelopment or vermis hypoplasia).[26] The authors indicated that cerebral calcification at the gray matter-white matter junction may help to differentiate ZIKV-induced microcephaly from microcephaly induced by TORCH (toxoplasmosis, other [syphilis, varicella zoster, parvovirus B19], rubella, cytomegalovirus, and herpes infections) infection (e.g., periventricular from cytomegalovirus infection). Therefore, many CNS image malformations can be detected by US and/or MRI imaging, with which pediatricians, neurologists, radiologists, and other professionals involved in the follow-up of those children should be familiarized.[53-57]

Microcephaly, a common neurological feature of CZS, has multiple definitions (epidemiology, postnatal, ultrasound, MRI, computed tomography, and postmortem), and each one has variability in the literature.[53,58] The common idea is that microcephaly refers to a smaller HC than should be detected for a given gestational period. In Brazil, the HC evaluation follows the INTERGROWTH-21st study for fetuses, the INTERGROWTH-21st study for infants, and the WHO criteria for long-term newborns.[59-61] Many reports were related to congenital ZIKV infection in fetuses and newborns with small head/brain series imaging findings.[62-66] Sarno et al.[24] described 52 fetuses with microcephaly and ZIKV infection associated with posterior fossa abnormalities, hydrocephalus, and ventriculomegaly, the last of these being described as a progressive lesion that leads to cerebral atrophy.[53-57,67-69]

Ocular involvement in infants with presumed CZS occurred more often in those with smaller cephalic diameters at birth and in infants whose mothers reported symptoms during the first trimester.[23] However, one infant did not have microcephaly, but had a chorioretinal scar on the macular region, indicating that microcephaly should not be a required criterion for CZS diagnosis and the ophthalmologic examination should be performed in all presumed cases of CZS.[70] The studies from different outbreak regions describe similar ocular findings, like mottling pigmentary maculopathy, macular chorioretinal atrophy, vascular tortuosity, a washed out peripheral retina with a hypolucent spot, peripheral pigmentary changes, clustered atrophic lesions, and subretinal hemorrhages. In these studies, the following were described as optic nerve findings: hypoplasia with the double-ring sign, pallor, increased cup-disk ratio,[21,24,42] optic nerve and peripapillary atrophy, tilted optic nerve, abnormal anterior segment findings like iris coloboma (atypical superior or temporal), microphthalmia, and cataract.[19] However, no ocular inflammation was seen in funduscopic examinations. In 2017, an ocular histopathologic study described features like pupillary membranes, immature anterior chamber angles, thinning of the retinal pigment epithelium, undifferentiated nuclear layers of the retina, perivascular inflammatory infiltrate choroidal thinning, and optic nerve atrophy and expression of ZIKV antigen in the iris, neural retina, choroid, and optic nerve.[16] The involvement of internal retinal and chorioretinal atrophy was shown by spectral domain optical coherence tomography.[71] A correlation between the ophthalmologic and neurological findings, as well as the attempt to standardize the syndrome and its correlation with other congenital infections, was made difficult by the lack of description, in many studies, of the neuroimaging and ophthalmologic findings of all patients, even due to initial stillbirth. However, among 10 studies, ocular findings were present in 20% patients with microcephaly, 33% patients with ventriculomegaly, and 43% patients with calcifications. Studying the calcification distribution pattern could help future studies to elucidate this correlation.

In our review, almost all fetuses and neonates exhibited severe neurological abnormalities, including microcephaly, abnormal cerebral volume, corpus callosum abnormalities, abnormal cortical formation, cerebral atrophy, ventriculomegaly, hydrocephalus, and/or cerebellar abnormalities.[19-38] What seems to be universal is that microcephaly is not the only finding, but that it is a serious consequence of progressive brain lesions, principally if infection occurs in the first trimester of gestation. Similarly, cortical abnormalities are frequently linked to progressive ventriculomegaly with abnormal growth of the posterior fossa and are responsible for cortical atrophy and posterior collapse of the skull with other malformations that characterize ZIKV microcephaly.[54,55]

There are limitations to our study. The number of reported neurological malformation cases could be repeatedly reported in some sequential studies; however, to avoid misinterpreting the data, duplicate information was excluded from the final sample of cases with ZIKV-related CNS damage. Our data, obtained from many databases and including published and unpublished data, revealed gaps in the literature. There were no meta-

analyses, clinical trials, or controlled studies on ZIKV and neurological malformations. The full range of neurological and developmental disabilities and many other adverse outcomes can only be determined with long-term follow-up studies that follow children with congenital ZIKV infections.

We conclude that the neurological and ocular malformations documented to date are sufficient to determine that vertical ZIKV infection can result in a full range of severe neurological malformations, including cerebral calcifications, ventriculomegaly, microcephaly (among others), ocular malformation, seizures, and neurodevelopment delay. Our current understanding of CZS allows for the distinction between ZIKV and other congenital infections. However, there is a gap in our knowledge of postnatal neurological and ophthalmologic long-term outcome.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pediatrneurol.2018.11.003.

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