SEVEN
publicações acadêmicas

Pathophysiological aspects, phenotype and early neurostimulation in patients with microcephaly secondary to Zika Virus

https://doi.org/10.56238/interdiinovationscrese-018

Cícera Luana Cruz Tavares
Resident Physician of Gynecology and Obstetrics at the Federal University of Cariri (UFCA/FAMEDE);
Graduated from the Estácio School of Medicine/FMJ
-Institution: Federal University of Cariri- UFCA/ FAMED
E-mail: Luana.smille@hotmail.com

Bruna Kerolayni Leite Cesário
Resident Physician of Gynecology and Obstetrics at the Federal University of Cariri (UFCA/FAMEDE);
Graduated from the Estácio School of Medicine/FMJ
Institution: Federal University of Cariri- UFCA/ FAMED
E-mail: brunakerolaynileite@gmail.com

Isabelly de Oliveira Pinheiro
Endocrinologist from the Walter Cantídio University Hospital - Federal University of Ceará (UFC) - RQE 1233
Internal Medicine from the Federal University of Cariri - RQE 10760
Graduated from the Estácio de Juazeiro do Norte School of Medicine (FMJ)
Professor at the Faculty of Medicine Estácio de Juazeiro do Norte (FMJ)
Master's student in Health Sciences at the Federal University of Cariri
Institution: Federal University of Cariri- UFCA/ FAMED
E-mail: isabellyop02@gmail.com

José Gilmar Sampaio Filho
Obstetrician and Gynecologist at Hospital das Clínicas - Federal University of Pernambuco - RQE 4277
Area of expertise in Fetal Medicine at Hospital das Clínicas - Federal University of Pernambuco - RQE 4278
Graduated from the Federal University of Campina Grande (UFCG)
Preceptor of the internship and medical residency at the Faculty of Medicine of the Federal University of Cariri
Institution: Federal University of Cariri
E-mail: gilsampaio@gmail.com

Camila Grangeiro Fernandes
Gynecologist and Obstetrician from the Federal University of Ceará, Barbalha Campus
Graduated from the Faculty of Medicine Estácio de Juazeiro do Norte (FMJ)
Professor at the Faculty of Medicine Estácio de Juazeiro do Norte (FMJ)
Institution: Federal University of Cariri- UFCA/ FAMED
E-mail: camilagrangeiro5@hotmail.com

Allana Maria Garcia Sampaio Cruz
Gynecologist and Obstetrician from the Federal University of Cariri - UFCA
Graduated from the Federal University of Cariri - UFCA
Institution: Federal University of Cariri- UFCA/ FAMED
E-mail: allanamariagarcia@gmail.com

ABSTRACT

The Zika virus (ZIKAV) is a flavivirus, which causes an arbovirus of epidemiological importance, mainly in tropical countries, which was first isolated in 1947 from a monkey in the Zika forest in Uganda and later in humans in Nigeria. In Brazil, in May 2015, ZIKAV infection was identified, which spread throughout the Americas and coincided with an increase in neurological complications such as congenital microcephaly and numerous cases of Guillain-Barré syndrome, an autoimmune disease that can cause acute flaccid paralysis, areflexia and ascending. Recently, some reports from the Brazilian Ministry of Health showed that cases of congenital microcephaly have increased among newborns in the northeastern region of the country, indicating a probable association with ZIKAV infection during pregnancy. The purpose of this study was to investigate in the literature the pathogenesis of microcephaly caused by ZIKAV and to present the phenotype of newborns affected by prenatal infection, prognosis and results of early neurostimulation of these affected newborns. It was prepared from a literature review in the VHL (Virtual Health Library) and PubMed (Medline) electronic databases. The search for the articles was restricted between 2009 and 2019. A search strategy was developed in Portuguese and English for each of the databases searched, using the following health descriptors: Zika virus, microcephaly and pathogenesis. The descriptors are in accordance with the Medical Subject Headings (MeSH) and Descriptors in Health Sciences (DeCS). Based on the review performed, ZIKAV infection during pregnancy appears to be the cause of a recognizable

pattern of congenital anomalies that is consistent and odd, although there are many similar components in other congenital infections there are some distinguishing features, among them severe microcephaly with partially collapsed skull, cerebral cortex with subcortical calcifications, macular scarring and pigmentary retinal spotting, congenital contractures, and early hypertonia with symptoms of extrapyramidal involvement. Based on the phenotype presented by these children, the treatment determined is individualized, and early neurostimulation is essential for better neuronal spasticity and to improve the quality of life of these newborns.

Keywords: Zika Virus, Microcephaly and pathogenesis.

1 INTRODUCTION

The Zika virus (ZIKAV) is a flavivirus, which causes an arbovirus of epidemiological importance, mainly in tropical countries, which was first isolated in 1947 from a monkey in the Zika forest in Uganda and later in humans in Nigeria (1,2). The first documented time occurred in the Yap Islands of Micronesia in 2007, however the largest of these was recorded in French Polynesia in the period between 2013 and 2014. ZIKAV has recently been introduced in the Americas and its transmission has been identified in several Brazilian states. (3,4,5)

ZIKAV is most often transmitted to humans through the bite of infected mosquitoes, called Aedes *aegypti and Aedes albopictus*, other less frequent forms of transmission are sexual or perinatal (6,7). Transmission of ZIKAV through blood transfusion has not yet been reported, but is likely to occur related from this route. Some studies have reported the infection and proliferation of ZIKAV in the blood-brain barrier, enabling the entry of ZIKV into the central nervous system (CNS). (8.9)

Classically, the clinical picture is similar to that of dengue and chikungunya, and is manifested by fever, headache, arthralgia of small joints such as hands and feet, myalgia and pruritic maculopapular rash, and non-purulent conjunctivitis (6). In addition, peripheral edema, retro-orbital pain, and gastrointestinal disturbances such as nausea and vomiting have also been observed, and symptoms last for approximately one week. (10)

In Brazil, in May 2015, ZIKAV infection was identified, which spread throughout the Americas and coincided with an increase in neurological complications such as congenital microcephaly and numerous cases of Guillain-Barré syndrome, an autoimmune disease that can cause acute flaccid paralysis, areflexia and ascending. Recently, some reports from the Brazilian Ministry of Health showed that cases of congenital microcephaly have increased among newborns in the northeastern region of the country, indicating a probable association with ZIKAV infection during pregnancy (11). By 2017, 10,039 cases had been reported as suspected, of which 2,106 were confirmed for microcephaly, 3,091 remained under investigation, and 4,842 were excluded. (12)

One of the congenital malformations characterized by inadequate brain development is microcephaly, which, by definition, is a head circumference less than two standard deviations from

normal for sex and gestational age, and can cause problems in its neuropsychomotor development. (13, 14). It is classified as primary, when detected before 36 gestational weeks, or secondary, when cases occur after delivery. (15). Depending on the age at which the episode occurs, certain sequelae can be seen, and the earlier the exposure, the greater the involvement and the greater the anomalies in the CNS. This disease is associated with necrosis, blockage of maturation and multiplication of neurons and as a consequence there are cortical deficits and proliferative defects. It can occur as an isolated condition or can be associated with signs and symptoms such as seizures, swallowing difficulties, motor and cognitive changes that will vary according to the degree of brain involvement and, in some cases, vision and hearing may be compromised. Genetic syndromes, fetal cerebral hypoxia-ischemic as well as other congenital or perinatal infections such as ZIKAV, these are TORCHS (Toxoplasmosis, Rubella, Cytomegalovirus, Herpes and Syphilis). (16, 17)

Currently, there is no specific treatment protocol to combat the infection caused by ZIKAV, only to prevent exposure. However, current evidence points to a causal relationship between ZIKAV infection during pregnancy and the increase in cases of microcephaly, but there are still insufficient data on the pathogenesis and events on which ZIKAV exerts its effects on the brain in intrauterine infection. Thus, the present study aimed to investigate in the literature the pathogenesis of microcephaly caused by ZIKAV and the presentation of the phenotype of newborns affected by prenatal infection, prognosis and results of early neurostimulation of these affected newborns.

2 MATERIALS AND METHODS

The study was based on a literature review of the electronic databases VHL (Virtual Health Library) and PubMed (Medline). The search for the articles was restricted between 2009 and 2019. A search strategy was developed in Portuguese and English for each of the databases searched, using the following health descriptors: Zika virus, microcephaly and pathogenesis. The descriptors are in accordance with the Medical Subject Headings (MeSH) and Descriptors in Health Sciences (DeCS).

The inclusion criteria used were the selection of studies that addressed pathophysiological aspects of microcephaly, phenotype of newborns, and prognosis and treatment. Exclusion criteria were epidemiology articles, interviews, and epidemiological reports.

After the selection of the articles, they were categorized according to the journal, year of publication, objectives, methodology used, and results. Then, the results were analyzed and discussed based on the literature.

3 RESULTS

The search in these databases resulted in 110 articles on the subject. The database with the highest number of publications was Pubmed, in which 78 articles were identified. The VHL database

contributed with 32 articles. After analyzing the titles and abstracts of the articles, 68 studies were excluded, so that only five studies met the pre-established criteria and were included in this review. The summary of the five articles can be found in table 1 below.

Table 1. Summary of the articles included in the review.

Author/year	Newspaper	Objective	Method/Sample	Results
Nunes et al, 2016	J. Pediatr.	His study aimed to critically review the literature available regarding the Zika virus outbreak in Brazil and its possible association with microcephaly cases.	Literature review regarding different aspects of the Zika virus outbreak in Brazil, such as transmission, epidemiology, diagnostic criteria, and its possible association with the increase of microcephaly reports. The PubMed search using the key word "Zika virus" in February 2016 yielded 151 articles.	The development of diagnostic techniques that confirm a cause–effect association and studies regarding the physiopathology of the central nervous system impairment should be prioritized. It is also necessary to strictly define the criteria for the diagnosis of microcephaly to identify cases that should undergo an etiological investigation.
Vargas et al, 2016.	Epidemiol. Serv. Health	describe the first cases of microcephaly possibly related to Zika virus in live born babies reported in the Metropolitan Region of Recife, Pernambuco State, Brazil.	His was a descriptive case series study (cases reported between August 1st and October 31st 2015), using medical record data and data from a questionnaire answered by the mothers of the babies.	The majority of the cases bore the characteristics of congenital infection; the clinical condition of the majority of mothers suggested Zika virus infection during pregnancy.
Ghouzzi VEL et al, 2016	Cell Death and Disease	Explored the possible similarities between transcriptional responses induced by ZIKV in human neural progenitors and those elicited by three different genetic mutations leading to severe forms of microcephaly in mice		. In agreement with these observations, we report that ZIKV infection increases total P53 levels and nuclear accumulation, as well as P53 Ser15 phosphorylation, correlated with genotoxic stress and apoptosis induction. Interestingly, increased P53 activation and apoptosis are induced not only in cells expressing high levels of viral antigens but also in cells showing low

				or undetectable levels of the same proteins.
Miranda Haas, 2016	Ophthalmology.	To describe the ocular findings of 3 cases of suspected congenital Zika viral infection with microcephaly and maculopathy.	Observational report of macular findings.	Zika virus has been linked to microcephaly in children of mothers with a viral syndrome during the first trimester of pregnancy. Ocular findings previously described a pigmentary retinopathy and atrophy that now can be expanded to include torpedo maculopathy, vascular changes, and hemorrhagic retinopathy. Ophthalmologic screening guidelines need to be defined to determine which children would benefit from newborn screening in affected regions.
Moore CA et al, 2017	JAMA Pediatr.	To inform pediatric healthcare providers who may be called upon to evaluate and manage affected infants and children, we review the most recent evidence to better characterize congenital Zika syndrome.	We reviewed published reports of congenital anomalies occurring in fetuses or infants with presumed or laboratory-confirmed intrauterine Zika virus infection. Congenital anomalies were considered in the context of the presumed pathogenetic mechanism related to the neurotropic properties of the virus.	Although the full spectrum of adverse reproductive outcomes caused by Zika virus infection is not yet determined, a distinctive phenotype-the congenital Zika syndrome-has emerged. Recognition of this phenotype by clinicians for infants and children can help ensure appropriate etiologic evaluation and comprehensive clinical investigation to define the range of anomalies in an affected infant as well as determine essential follow-up and ongoing care.

4 DISCUSSION

ZIVAK has neurotropism, especially microcephaly, as an important complication. It has been related to prenatal infection by ZIKAV and its infectivity power includes the entire gestational period, including peripartum (18, 19). Brazil was the first country to identify a possible relationship between ZIKAV infection in pregnancy and the occurrence in newborns with microcephaly, and the first documented cases came from the Pernambuco region and subsequently throughout the Brazilian Northeast from the second half of 2015. A relevant fact in the retrospective studies is that most of the mothers presented symptoms related to ZIKAV infection during the gestational period, such as fever of up to 38.5º, pruritic maculopapular erythema, and non-purulent conjunctivitis

leading researchers to suggest the possibility of mother-to-child transmission of ZIKV leading to neurological disorders (20, 21). One of the measures adopted and indicated by the Ministry of Health in the protocol for the care of microcephaly cases in Brazil was the ZIKAK test with RT-PCR to be collected from the blood and urine of pregnant women to screen for infection in pregnant women older than 5 days with fever and skin rash (29).

A relevant fact is that during the outbreak of infection in the northeastern region of Brazil, through an amniocentesis, ZIKAV was identified in the amniotic fluid of two pregnant women, proving that the virus can cross the placental barrier and cause infection in the developing fetus. The screening test during prenatal care is morphological ultrasound from the 20th week of gestation, and as a suggestive aspect of intrauterine infection, they present cerebral calcifications in parenchitemmatous and periventricular regions and areas of the thalamus and basal ganglia, agenesis of the corpus callosum, alterations of the posterior fossa and ventricle megaliga exvacum accompanied by cerebral atrophy culminating in significant craniofacial disproportion (3, 22, 23)

The infection can occur throughout the gestational period and current research reveals that there is blockage of maturation and migration of cortical neurons, consequently if the infection occurs earlier, that is, in the period of embryogenesis in which important structures are still in formation, there is greater structural and, consequently, functional involvement of the fetus. The brain pathology of newborns affected by ZIKAV infection closely resembles the neuropathology associated with cytomegalovirus, the most notable difference is the distribution of intracranial calcifications, in which ZIKAV infections are typically subcortical and periventricular in CMV (24). Such calcifications are probably dystrophic and related to cell death by activation of the P53 protein causing necrosis, apoptosis, or both (25, 26, 27).

Other Characteristic is the structural ocular anomaly such as cataracts, intraocular calcifications and special attention to chorioretinal atrophy, focal retinal pigment spots and optic nerve atrophy anomalies not evidenced in other congenital viral infection. The pathogenesis of ocular lesions is still unknown, there is a possible direct cellular damage by ZIKAV as well as by inflammatory sequelae

(42). Active chorioretinitis, a possible predecessor of chorioretinal atrophy (28, 29, 30-35). Retinal lesions including well-defined chorioretinal atrophy and macroscopic pigmentation, usually affecting the macular region, are unique to ZIKAV infection (32).

Neurogenic factors that affect the corticospinal tract, motor neurons, or their interactions can cause fetal motor abnormalities, leading to decreased movement and contractures involving one or more fetal joints, termed arthrogryposis multiple congenita. (36, 42). As a consequence, there are articular contractures, but this mechanism is not well understood, case studies and case series show the presence of clubfoot, bilateral congenital hip dislocation, partial or total knee dislocation (30, 37 and 38).

Regarding the prognosis of these children, there are few medical results in the literature, it is known that development is severely compromised. Three infants born after the ZIKAV outbreak in French Polynesia and presumed infected in utero had severe neurological sequelae, including motor and cognitive impairments, seizures, and swallowing difficulties that lead to failure to thrive; One infant had severe vision loss and suspected hearing loss (36). Profound sensorineural hearing loss has been reported in one child with characteristic brain imaging findings and positive CSF for ZIKAV IgM, (37) and documented sensorineural hearing loss in 4/69 infants with microcephaly and laboratory evidence of congenital ZIKAV infection (38). Examination of affected infants showed hypertonia and spasticity, irritability manifested by excessive crying, dysphagia and, less frequently, hypotonia.35,36 Abnormal electroencephalogram activity was observed in 48% of infants with congenital congenital ZIKAV infection and 52% had focal or multifocal discharges.36. In addition, tremors and postures consistent with extrapyramidal dysfunctions have been reported (39,40-42).

5 CONCLUSION

Based on the review performed, ZIKAV infection during pregnancy appears to be the cause of a recognizable pattern of congenital anomalies that is consistent and odd, although there are many similar components in other congenital infections there are some distinguishing features, among them severe microcephaly with partially collapsed skull, cerebral cortex with subcortical calcifications, macular scarring and pigmentary retinal spotting, congenital contractures, and early hypertonia with symptoms of extrapyramidal involvement. Based on the phenotype presented by these children, the treatment determined is individualized, and early neurostimulation is essential for better neuronal spasticity and to improve the quality of life of these newborns.

REFERENCES

Pinto Junior VL, Luz K, Parreira R, Ferrinho P. Vírus Zika: Revisão para clínicos. Acta Med Port. 2015; 28 (6):760-65.

Musso D, Nhan T, Robin E, Roche C, Bierlaire D, Zisou K, et al. Potential for Zika virus transmission through blood transfusion demonstrated during an outbreak in French Polynesia, November 2013 to February 2014. Euro Surveill. 2014;19(14):1-3.

Calvet G, Aguiar RS, Melo ASO, Sampaio SA, de FilippisI, Fabri A, et al. Detection and sequencing of Zika vírus from amniotic fluid of fetuses with microcephaly in Brazil: a case study. Lancet Infect Dis. 2016;16(6):653-60.

Mlakar J, Korva M, Tul N, Popovic M, Poljsak-Prijatelj M, Mraz J, et al. Zika vírus associated with microcephaly. N Engl J Med. 2016;374:951-58.

Cunha MS, Esposito DLA, Rocco IM, Maeda AY, Vasami FGS, Nogueira JS, et al. First complete genome sequence of zika vírus (flaviviridae, flavivirus) from an autochthonous transmission in Brazil. Genome Announc. 2016; 4 (2): e00032-16.

Chen HL, Tang RB. Why zika virus infection has become a public health concern? J Chin Med Assoc. 2016; 79(4):174-78.

Petersen E, Wilson ME, Touch S, McCloskey B, Mwaba P, Bates M, et al. Rapid spread of zika virus in the Americas – implications for public health preparedness for mass gatherings at the 2016 Brazil Olympic Games. Int J Infect Dis. 2016;44:11-5.

Petersen LR, Jamieson DJ, Powers AM, Honein MA. Zika virus. N Engl J Med. 2016; 374: 1552-63.

Nunes ML, Carlini CR, Marinowic D, Neto FK, Fiori HH, Scotta MC, et al. Microcephaly and zika virus: a clinical and epidemiological analysis of the current outbreak in Brazil. J Pediatr. 2016; 92(3): 230-40.

Basarab M, Bowman C, Aarons E, Cropley I. Zika virus. BMJ. 2016; 352: i1049.

Cauchemez S, Besnard M, Bompard P, Dub T, Guillemette-Artur P, Eyrolle-Guignot D, et al. Association betweenzika vírus and microcephaly in French Polynesia, 2013-2015: a retrospective study. Lancet. 2016;387:2125-32.

Brazil - Ministério da Saúde. Centro de Operações de Emergência em saúde pública sobre microcefalias. Informe epidemiológico nº50 – Semana Epidemiológica (SE) 43/ 2016 (23/10/2016 a 29/10/2016). Monitoramento dos casos de microcefalia no Brasil. Brasília: Ministério da Saúde; 2016.

Vargas A, Saad E, Dimech GS, Santos RH, Sivini MAVC, Albuquerque LC, et al. Características de los primeiros casos de microcefalia , posiblemente relacionadas con el vírus Zika reportados em la Región Metropolitana de Recife. Epidemiol Serv Saúde. 2016;25(4):691-700.

Ashwal S, Michelson D, Plawner L, Dobyns WB. Practice parameter: evaluation of the child with microcephaly (an evidence – based review). Neurology. 2009; 73(11):887-97.

Anaya JM, Ramirez-Santana C, Salgado-Castaneda I, Chang C, Ansari A, Gershwin ME. Zika vírus and neurologic autoimmunity: the putative role of gangliosides. BMC Med.

2016; 14(1):1-3.

Gilmore EC, Walsh CA. Genetic causes of microcephaly and lessons for neuronal development. Wires Dev Biol. 2013; 2:462-78.

Garcez PP, Loiola EC, da Costa RM, Higa LM, Trindade P, Delvecchio R, et al. Zika virus impairs growth in human neurospheres and brain organoids. Science. 2016; 352:816-18.

Liang Q, Luo Z, Zeng J, Chen W, Foo SS, Lee SS, et al. Zika virus NS4A and NS4B proteins deregulate Akt-Mtor signaling in human fetal neural stem cells to inhibit neurogenesis and induce autophagy. Cell Stem Cell. 2016; 19(5):663-71.

Rasmussen SA, Jamieson DJ, Honein MA, Petersen LR. Zika virus and birth defects – reviewing the evidence for causality. N Engl J Med. 2016; 374(20):1981-87.

De Carvalho NS, De Carvalho BF, Fugaça CA, Dóris B, Biscaia ES. Zika virus infection during pregnancy and microcephaly occurrence: a review of literature and Brazilian data. Braz J Infect Dis. 2016; 20(3):282-89.

Vasconcelos PFC, De Oliveira CS. Microcephaly and Zika virus. J Pediatr (Rio J). 2016; 92(2):103-05.

Mawson AR. Pathogenesis of Zika virus – associated embryopathy. BioRes Open Acess. 2016; 5(1):171-76.

Schuler-Faccini L, Ribeiro EM, Feitosa IML, Horovitz DDG, Cavalcanti DP, Pessoa A, et al. Possível associação entre a infecção pelo vírus zika e a microcefalia – Brasil, 2015. Weekly. 2016; 65(3):1-4

Averill LW, Kandula VV, Akyol Y, Epelman M. Fetal brain magnetic resonance imaging findings in congenital cytomegalovirus infection with postnatal imaging correlation. Semin Ultrasound CT MR. 2015; 36(6):476–486. [PubMed: 26614131]

Ghouzzi VEL, Bianchi FT, Molineris I, Mounce BC, Berto GE, Rak M, et al. ZIKA vírus elicits P53 activation and genotoxic stress in human neural progenitors similar to mutations involved in severe forms of genetic microcephaly and P53. Cell Death Dis. 2016; 7(10): e2440.

Breuss M, Fritz T, Gstrein T, Chan K, Ushakova L, Yu N, et al. Mutations in the murine homologue of TUBB5 cause microcephaly by perturbing cell cycle progression and inducing p53-associated apoptosis. Development. 2016; 143:1126-33.

Marjanovic M, Sánchez-Huertas C, Terré B, Gómez R, Scheel JF, Pacheco S, et al. CEP63 deficiency promotes p53-dependent microcephaly and reveals a role for the centrosome in meiotic recombination. Nat Communic. 2015; 6(7676):1-14.

Paula Freitas B, Oliveira Dias JR, Prazeres J, et al. Ocular findings in infants with microcephaly associated with presumed Zika virus congenital infection in Salvador, Brazil. JAMA Ophthalmol. 2016 Feb 9. [Epub ahead of print].

Miranda HA 2nd, Costa MC, Frazao MA, Simao N, Franchischini S, Moshfeghi DM. Expanded spectrum of congenital ocular findings in microcephaly with presumed Zika infection. Ophthalmology. 2016; 123(8):1788–1794. [PubMed: 27236271]

Schuler-Faccini L, Ribeiro EM, Feitosa IM, et al. Possible association between Zika virus infection and microcephaly — Brazil, 2015. MMWR Morb Mortal Wkly Rep. 2016; 65(3):59–62. [PubMed: 26820244]

Van der Linden V, Filho EL, Lins OG, et al. Congenital Zika syndrome with arthrogryposis: retrospective case series study. BMJ. 2016; 354:i3899.doi: 10.1136/bmj.i3899 [PubMed: 27509902]

Ventura CV, Maia M, Travassos SB, et al. Risk factors associated with the ophthalmoscopic findings identified in infants with presumed Zika virus congenital infection. JAMA Ophthalmol. 2016; 134(8):912–918. [PubMed: 27228275]

Ventura CV, Maia M, Ventura BV, et al. Ophthalmological findings in infants with microcephaly and presumable intra-uterus Zika virus infection. Arq Bras Oftalmol. 2016; 79(1):1–3. [PubMed: 26840156]

Brasil P, Pereira JP Jr, Raja Gabaglia C, et al. Zika virus infection in pregnant women in Rio de Janeiro – preliminary report. N Engl J Med. 2016 Mar 4. [Epub ahead of print].

Valentine G, Marquez L, Pammi M. Zika virus-associated microcephaly and eye lesions in the newborn. J Pediatric Infect Dis Soc. 2016; 5(3):323–328. [PubMed: 27405738]

Kowalczyk B, Felus J. Arthrogryposis: an update on clinical aspects, etiology, and treatment strategies. Arch Med Sci. 2016; 12(1):10–24. [PubMed: 26925114

Garcez PP, Loiola EC, Madeiro da Costa R, et al. Zika virus impairs growth in human neurospheres and brain organoids. Science. 2016

Ventura CV, Maia M, Bravo-Filho V, Gois AL, Belfort R Jr. Zika virus in Brazil and macular atrophy in a child with microcephaly. Lancet. 2016a; 387(10015):228.

Schuler-Faccini L, Ribeiro EM, Feitosa IM, et al. Possible association between Zika virus infection and microcephaly — Brazil, 2015. MMWR Morb Mortal Wkly Rep. 2016; 65(3):59–62. [PubMed: 26820244]

Besnard M, Eyrolle-Guignot D, Guillemette-Artur P, et al. Congenital cerebral malformations and dysfunction in fetuses and newborns following the 2013 to 2014 Zika virus epidemic in French Polynesia. Euro Surveill. 2016; 21(13)

Leal MC, Muniz LF, Neto SS, Linden V, Ramos RC. Sensorineural hearing loss in a case of congenital Zika virus. Braz J Otorhinolaryngol. 2016 Jun 30. [Epub ahead of print].

Leal MC, Muniz LF, Ferreira TS, et al. Hearing loss in infants with microcephaly and evidence of congenital Zika virus infection – Brazil, November 2015-May 2016. MMWR Morb Mortal Wkly Rep. 2016; 65(34):917–919. [PubMed: 27585248]

Culjat M, Darling SE, Nerurkar VR, et al. Clinical and imaging findings in an infant with zika embryopathy. Clin Infect Dis. 2016; 63(6):805–811. [PubMed: 27193747]

Schuler-Faccini L, Ribeiro EM, Feitosa IM, et al. Possible association between Zika virus infection and microcephaly — Brazil, 2015. MMWR Morb Mortal Wkly Rep. 2016; 65(3):59–62. [PubMed: 26820244]

Silva AAM, Ganz JSS, Sousa PS, et al. Early growth and neurologic outcomes of infants with probable congenital Zika virus syndrome. Emerg Infect Disease. 2016 Nov. [Aug 25]. doi: 10.3201/eid2211.160956

Moore CA, Staples JE, Dobyns WB, Pessoa A, Ventura CV, Fonseca EB, Ribeiro EM, Ventura LO, Neto NN, Arena JF, Rasmussen SA et al. Characterizing the Pattern of Anomalies in Congenital Zika Syndrome for Pediatric Clinicians. JAMA Pediatr. 2017 Mar 1;171(3):288-295. doi: 10.1001/jamapediatrics.2016.3982.