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Microcephaly and ZIKA Virus: Certainty or Presumption? Systematic Review

Microcefalia y Virus Zika: ¿Certeza o Presunción? Revisión Sistemática

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Abstract

The Zika virus has been associated with microcephaly since 2015 with established links based on the epidemic in Brazil, which affected several pregnant women. The purpose of this research was to demonstrate the link between Zika virus and microcephaly, through the analysis of the characteristics related to the virus, the theories of how it enters the organism and the clinical manifestations, which lead to neurological affectations. This is a descriptive, and transversal research. The main sources of information come from studies in various medical journals, which support the proposed ideas. Some proper virus characteristics were described, as: neurotropism, the capacity to cross the placental barrier and the ability to produce degeneration of the neuroprogenitor cells, which are complement to the above-mentioned theories. Likewise, molecular alterations in the structure of the virus, allowing the virus to interfere with the brain development of fetus in pregnant women. The clinical manifestation that produces Zika virus is called Severe Congenital Syndrome which includes manifestations in the newborn, such as, morphology of the skull, brain anomalies, congenital contractures and neurological sequelae. All the damage shown have been identified, thanks to neurological examinations to newborn, neuroimaging studies, neuropathology to the cranium and its tissue.

Keywords: stem cells, fetal growth retardation, mutation, zika virus

Resumen

El virus Zika se ha asociado con la microcefalia desde 2015 con vínculos establecidos con la epidemia en Brasil, que afectó a varias mujeres embarazadas. El objetivo de esta investigación fue demostrar el vínculo entre el virus Zika y la microcefalia, a través del análisis de características relacionadas con el virus, teorías de cómo ingresa al organismo y las manifestaciones clínicas, que conducen a afecciones neurológicas. Esta es una investigación descriptiva y transversal. Las principales fuentes de información provienen de estudios en varias revistas médicas, que respaldan las ideas propuestas. Se describieron algunas características propias del virus, como neurotropismo, la capacidad de cruzar la barrera placentaria y producir degeneración de las células neuroprogenitoras, un complemento de las teorías mencionadas anteriormente. Asimismo, las alteraciones moleculares en la estructura del virus, lo que permite que el virus interfiera con el desarrollo cerebral del feto en mujeres embarazadas. La manifestación clínica que produce virus Zika se llama Síndrome congénito severo, que incluye manifestaciones en el recién nacido, como morfología del cráneo, anomalías cerebrales, contracturas congénitas y secuelas neurológicas. Todos los daños mostrados han sido identificados, gracias a exámenes neurológicos a recién nacidos, estudios de neuroimagen, neuropatología del cráneo y su tejido.

Palabras claves: células madre, retardo del crecimiento fetal, mutación, virus zika

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Introduction

Zika virus (ZIKV) is an arbovirus transmitted by the *Aedes aegypti* mosquito bite. It was first isolated in the forests of Zika (Uganda) from a Rhesus monkey [1]. Then in 1968, from humans in Nigeria, Uganda and Senegal [2].

In 2007, the first outbreak of infection was documented in Micronesia (island of Yap), with 185 suspected cases reported, of which 49 (26%) were confirmed as proven cases and 59 (32%) as probable cases, and *Aedes hensilii* was identified as the vector [3]. The outbreak lasted 13 weeks. In 2013, another outbreak was recorded in French Polynesia, where approximately 10,000 cases were reported, 70 of them severe and associated with neurological complications or autoimmune disease [4]. In this situation, the identified vectors were the mosquitoes *Aedes aegypti* and *Aedes polynesiensis* [5]. During the outbreak of ZIKV disease in this region, it was reported an increase in cases of Guillain Barré syndrome, a neurological paralysis that is linked to immune disruption generated by viruses, vaccines and/or environmental toxins [6].

Later, in 2014, ZIKV arrives in America to Easter Island, Chile, where a case was presented; this patient, native of the place, had traveled to an art fair in Tahiti; upon his return, he presented a feverish picture and the analysis sent to Santiago, Chile, confirmed Zika's diagnosis [7].

Therefore, the Asian lineage of ZIKV is the one that circulates in Brazil and then in the Americas, according to the sequencing carried out by Pasteur Institute in Dakar [8]. A hypothesis of how it was probably entered due to the visit of several tourists, for the World Cup of Football in 2014, contributing to the infection of ZIKV [9]. In Brazil, the first 16 confirmed cases were reported on May 15, 2015 [10]. The cases occurred in the states of Bahia and Rio Grande do Norte, as well as in the northeast of the country, with eight cases reported accordingly. The alarm was raised when in October 2015, pregnant women affected by this new condition appeared in the country, presenting children with microcephaly and disability [11].

Other findings related to acute infection include low back pain, epigastralgia, anorexia, dry cough, paresthesias in extremities, ascending muscle weakness, pelvic limb areflexia, orthostatic hypotension, photophobia, hematospermia, dysuria, perineal pain, prostatitis, hand and ankle edema and subcutaneous bleeding [12].

Up to January 29 2016, 25 countries and territories in the Americas had reported local transmission of the virus (indigenous cases): Barbados, Bolivia, Brazil, Colombia, Costa Rica, Curaçao, Dominican Republic, Ecuador, Guyana, El Salvador, French Guyana, Guatemala, Guadeloupe, Haiti, Honduras, Martinique, Mexico, Nicaragua, Panama, Paraguay, Puerto Rico, Saint Martin, Suriname, Virgin Islands and Venezuela [4].

In Ecuador, during January 2016, the first two laboratory-confirmed cases of ZIKV infection were reported. The patients were Ecuadorians living in Quito, with a history of traveling to Neiva, a city in Colombia, who presented exanthema, pruritus, fever, headache, generalized joint pain and conjunctival hyperemia. A total of 965 cases of pregnant women with ZIKV infection were reported for the three-year period 2016-2018. In 2016, 242 cases were reported, by 2017, 722 cases were reported and by 2018, a case in pregnant women corresponding to epidemiological week (EW) 14. In relation to gestational age, the following were reported: 136 cases corresponding to a patient with gestational age less than 12 weeks, 420 cases with gestational age greater than 21 weeks and 167 cases with gestational age higher than 28 weeks. Also, by 2016, until EW 14 in 2018, 17 children with vertical transmission of Zika, without congenital malformation, were registered. These children were the product of positive women and suspected ZIKV infection, proceeding from the provinces: Manabí, Guayas, El Oro and Santo Domingo de los Tsachilas [13].

With regard to the notification of Congenital Syndromes; 20 cases of microcephaly associated with ZIKV and 1 case of congenital malformation without microcephaly have been reported; according to the province of residence they are distributed as follows: 5 cases in Manabi, 2 in Los Rios, 8 in Guayas, 1 in Santo Domingo de los Tsachilas, 2 in Pichincha, 1 in Sucumbios and 2 in El Oro. Also, five cases of inconclusive congenital malformations have been identified, coming from Guayas, Esmeraldas and Manabí. These newborns are in the process of being investigated. New cases have not been reported until SE 14 in 2018 [13].

Regarding studies related to this topic, Chavali et al. [14] state that ZIKV captures a human protein called Musashi-1 (MSI1), for its own replication, preventing the protein from working properly and altering the expression of many genes involved in neuronal development. Additional findings mention that all MSI1 proteins in the developing embryo are produced by the neural stem cells that will eventually become the infant's brain, which may be the reason for why these cells are so vulnerable. On the other hand, authors such as Gascon-Jiménez et al. [15] confirm the existence of subjects with a rare type of inherited microcephaly (primary recessive autocephaly) unrelated to ZIKV infection.

In this sense, while the majority of infections caused by this virus remain undetected and have only minor consequences, effects on pregnant women and newborns are becoming a serious global problem of concern for public health [16]. This investigation arises from the fact that ZIKV infection is directly related to an increase in abortions and the possibility that children, born to mothers who have acquired the virus, may present neurological anomalies, convulsive syndromes and mental retardation [17]. Therefore, postnatal surveillance or monitoring of children in women who have suffered from ZIKV infection during pregnancy is necessary [18].

This review consists in establishing the relationship between ZIKV and the presence of microcephaly coming from pregnant women who acquired the virus, possible

theories of how the virus enters the fetus, as well as identifying the causes of microcephaly, structural damage (histological and molecular) as well as recognizing the clinical manifestations in the newborn affected by ZIKV.

Methods

The research methodology was structured as follows:

Information sources and database: this article is based on a direct review with access to the following databases: Scielo (www.scielo.org), Pubmed (www.ncbi.nlm.nih.gob/pubmed), ScienceDirect (www.sciencedirect.com), Science (https://science.sciencemag.org), Neurology (www.neurologia.com), offered by the Google platform, using the following descriptors: Zika virus, ZIKAV, microcephaly and pregnancy. Articles published by the UN (http://apps.who.int) were also considered. In the search engine bar of each repository the following search equations were used as filters for the derivation of articles: "Zika and pregnancy", "Zika and microcephaly", "Zika in pregnant women", "Zika and neurological effects", "Physiopathogy and Zika".

Eligibility criteria: articles published from 2015 to December 2019 were considered. Within the inclusion criteria, the following were considered: a) articles from primary sources published in indexed journals, with a review nature, original research articles, comparative studies, evaluation studies and meta-analysis; b) articles in English and Spanish: c) articles that addressed the relationship between the presence of microcephaly in pregnant women with Zika and how the virus is transferred to the neonate, d) articles that used methods and technologies of a biochemical and molecular nature to detect the presence of the virus in brain tissues. The following were excluded: a) guides, letters to the editor, editorials, theses, dissertations, b) Bibliographic material only available in physical form, and c) articles published before 2015.

Additional criteria: To collate the different articles, a critical reading of each abstract and a general evaluation of the full text were made, considering the most important elements such as the methodology used, results and conclusions (Figure 1). This bibliographic review did not evaluate the methodological quality of the studies, but rather to verify the theories that described the cause of microcephaly in the newborn, the structural data, both histological and molecular, and the clinical manifestations of the newborn affected by ZIKV.

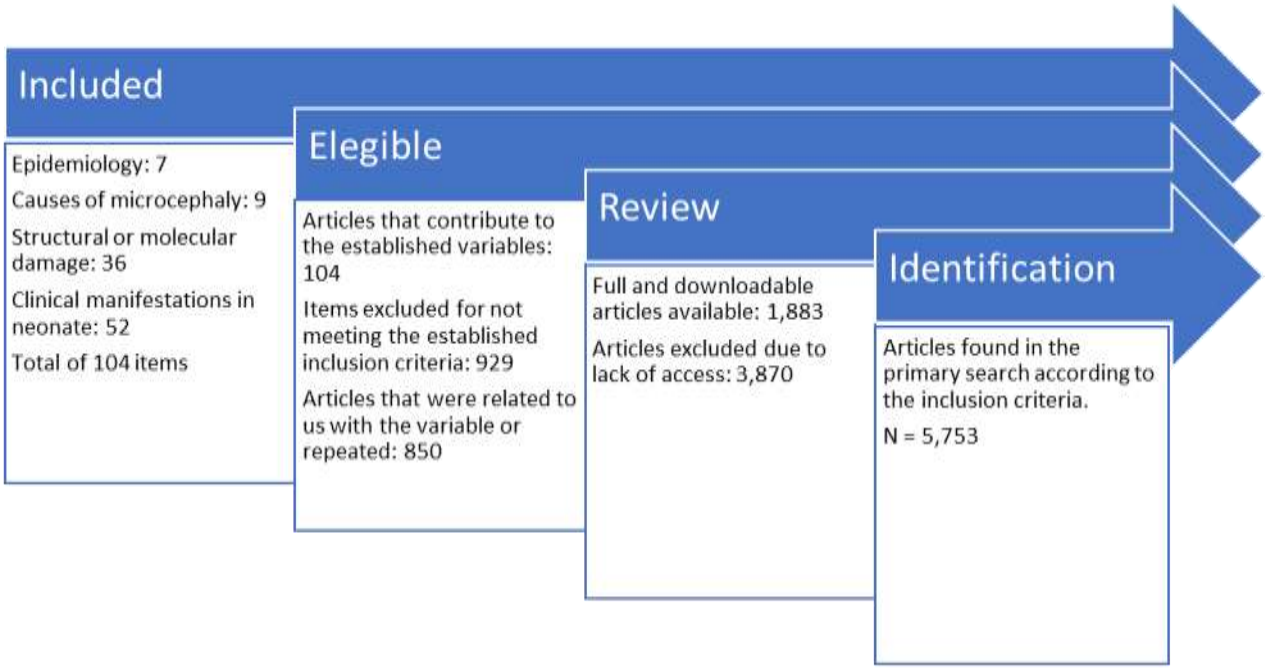

Figure 1. Methodological sequence of the research. Source: Own elaboration.

Results

Relationship between ZIKV and Microcephaly

Microcephaly is considered a structural defect in which the fetus or infant has a smaller head size than expected when compared to others of similar gestational age and sex [19]. It is determined by the head circumference (HC) which is -2 SDE (standard deviations) below the mean for age and sex [20]. This abnormality can also occur when a pregnant woman is exposed to radiation, tobacco, alcohol and certain viruses (including cytomegalovirus and ZIKV) [21].

In this regard, two outbreaks confirm the link between microcephaly and ZIKV infection. Those are: the first outbreak, which occurred in French Polynesia in 2014, involving 17 cases of newborns with microcephaly [22]. In this epidemic, pregnant women did not present symptoms of having ZIKV infection; however, IgG antibodies against flavivirus (Dengue) were found, in serology, which may have been asymptomatic mothers [23]. In contrast, in the second outbreak, which occurred in Brazil in October 2015, the presence of antigens was confirmed in the chorionic villi of placentas in the first trimester. Likewise, the tissues investigated were positive for ZIKV RNA by RT-PCR [24]. In addition, pregnant women presented itching and arthralgia which are characteristic features of ZIKV infection, during the first trimester [25]. These events caused the World Health Organization (WHO) to declare a state of alert and all its 140 member countries to register any ZIKV cases and to pay due attention. From that moment, studies linking ZIKV to microcephaly began [26]. Another study recorded the genomic sequence of the virus taken from fetal brain tissue in a pregnant woman who showed ZIKV symptoms at the end of the first trimester of pregnancy, which was the thirteenth week of gestation. This phylogenetic study showed a high coincidence of 99.7% with the genome of the virus isolated from French Polynesia in 2013 as well as from Brazil, in Sao Paulo, in 2015. Given the outbreak originated in Brazil, this country has shown the highest prevalence of microcephaly [27]. Mutations in three proteins were highlighted: NS1, responsible for immune system evasion; NS4B, inhibition of the response of interferon type I and NS5, the masking of viral RNA in the host [28]. Especially, the NS5 protein mutation which facilitated viral replication in human cells, and that same mutation was found in different countries of America [29].

Theories

Three hypotheses are presented as to how ZIKV might infect the fetus. The first hypothesis considers that it occurs through receptor-mediated endocytosis, which can be DC-SIGN, TIM and TAM proteins (AXL and Tyro3). Of which, it was proved that AXL and Tryro3 are the ones that give the virus more accessibility to enter the cells and start the replication process [30]. The AXL receptor, which is expressed by radial glial cells, astrocytes and microglia during the development of the human cortex, is the main entry factor for ZIKV and once it crosses the placental barrier, it becomes neurotrophic [31]. The second hypothesis suggests transport with maternal antibodies, which are transferred to the fetus [32]. However, this theory was discarded because it did not coincide with the most likely time in which the infection occurs which is during the first or second trimester and infecting the placenta directly [33]. Finally, the third hypothesis is due to the fact that ZIKV infection of the placenta can lead to a generalized immune reaction and cause inflammatory cytokines to activate microglia and these cause disruptions of neurogenesis. Also, reducing the neuronal development, predisposing to the appearance of microcephaly [34]. On the other hand, studies mention that the placenta synthesizes and secretes molecules that are essential for the development of the brain, ZIKV interrupts its secretion, and is propitious to produce mutations among these, the genes of microcephaly, overexpressing them [35].

Characteristics

ZIKV shows three important characteristics, these are: it possesses a neurotropism [36], it infects astrocytes and neural matrix cells; it crosses the placental barrier [37] and by invading the hippocampus and meninges it causes degeneration of neuroprogenitor cells and immature cortical neurons [38].

The neurotropism that ZIKV has in order to attack the neural cells evidenced by being efficiently replicated in the brain tissue of an embryonated mouse, where using cellular markers, proved that the virus affects directly the progenitor cells and radial glial cells. Causing the deregulation of the processes of proliferation, differentiation and development of the organ [36]. On this regard, the authors found high levels of viral particles in the ventricular and sub-ventricular areas, where gliaradial cells and new neurons reside. In addition, nests of infected radial glial cells were detected in the germinal zone, mainly affecting neuronal migration, and expanding the infection to their descendant cells, which are neurons and astrocytes (Figure 2) [39].

Another feature is that ZIKV crosses the placental barrier, and thereby infecting the fetus, causing damage in the brain development [37]. The detection of ZIKV in the amniotic fluid of two pregnant women from Paraiba state in Brazil, whose fetuses were positive for diagnosis with microcephaly, confirms this characteristic [40]. Also, researches on human placental cells from in vitro infections shows that ZIKV replicates in placental macrophages (Hofbauer cells), trophoblasts and endothelial fetal cells that induce the expression of antiviral genes [41]. Primary trophoblasts (placental cells) produce a type III interferon (IFN) IFNλ1 that acts as an antiviral, protecting placental epithelial cells from ZIKV infection [42]. However, the person becomes more susceptible during the first trimester because the trophoblasts are still developing, opening the way for a greater probability of infection, as opposed to later in the pregnancy when the protection offered by the interferon is already in place [43]. This being the case, the placenta in

an advanced stage of pregnancy can protect the fetus and block the transfer of the virus and provide its own inflammatory response. Therefore, the periods of greatest risk for the presence of microcephaly occur in the pre-conception period, the first trimester during the period of proliferation, differentiation and migration of neuroepithelial tissue [44].

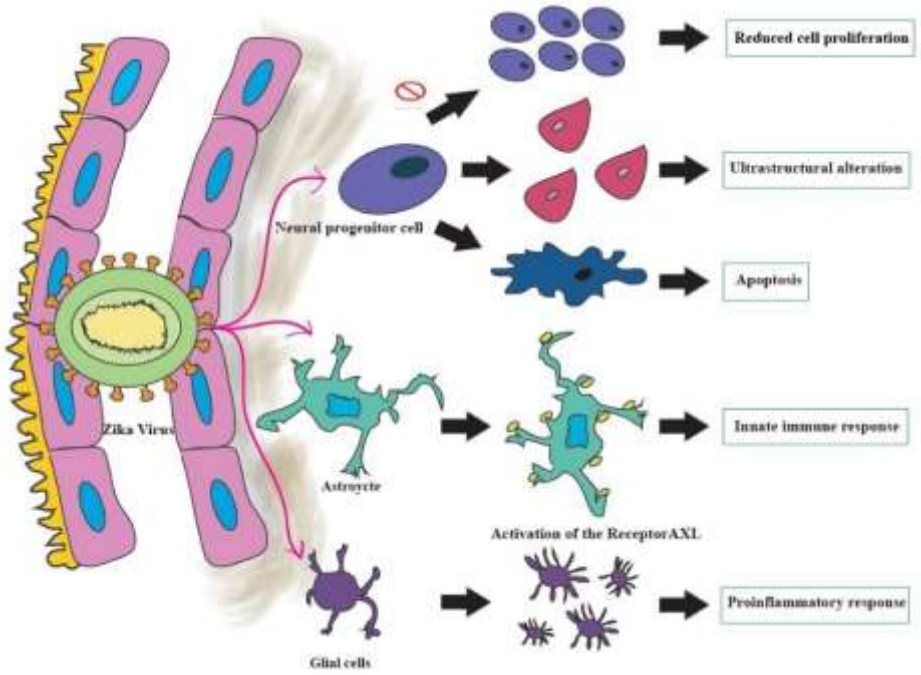

Figure 2. Main cells affected by the ZIKV and consequences. Source: Own elaboration.

As for the last feature, ZIKV has been shown to induce apoptosis and autophagy in mice neural tissue [38]. On pathological examination of a ZIKV-infected fetus in utero, diffuse astrogliosis and activation of the microglia cells present was observed [45]. Also, it affects the genes that regulate cytokine production and the regulation of apoptotic pathways, interestingly, the cells of the cranial neural crest, also a degree of apoptosis after ZIKV infection, by releasing a cytokine in response to viral infection; causing cell death and aberrant neurogenesis for the neural progenitor cells [46]. One of the affected pathways is the PI3K-Akt-mTOR, by the cooperation of the viral proteins NS4A and NS4B, and the inhibition of mTOR in neuronal development produces microcephaly, promotes autophagy, in a way that causes synergism with the promotion of viral replication [47].

Effects on the newborn

The ZIKV has the ability to cross the placental barrier, which allows it to feed on amniotic fluid, the site that contains the fetus during its development, resulting in damage in brain formation [48].

In most cases of congenital ZIKV infection these damages have been found as an additional finding and not specifically as microcephaly. Ultrasound suggests that there is a relationship between a recent pathology and ZIKV infection, differentiating it from other congenital infections [49]. This is a new and severe congenital syndrome, which has been called Congenital Zika Syndrome (CZS), characterized by neurological damage and massive reduction of intracranial volume with ventriculomegaly [50].

The most common clinical manifestations that have been identified in infants with CZS are: microcephaly, decreased brain tissue, optical damage, pigment changes, limited joint movement, central nervous system malformation and muscular hypertonicity [51]. Children born with CZS at approximately 2 years of age show evidence of developmental delay, and as a result of the sequelae of the syndrome, constant and lifelong medical attention is required [52]. However, severe affectations only appear in approximately 10% of infants with infected mothers [53].

Neonates suffering from CZS can then be classified into structural and functional affectations. The structural ones include cranial morphology, ocular anomalies, cerebral anomalies and congenital contractures. The functional alterations are linked to neurological wear, reduced intrauterine growth and a birth weight less than 2,500g [28].

Cranial morphology: for the babies diagnosed with microcephaly, the size of the head correlates with the underlying brain size, i.e. if microcephaly is present it is an indication that the brain has not developed properly or

that growth has stopped. Even so, these measurements do not consistently predict long-term sequelae [27].

Severe microcephaly, when there are three or more standard deviations below the mean, is manifested in congenital ZIKV infection, to this is commonly added the superimposed cranial suture, prominence of the occipital bone and furrows in the scalp due to excess skin [54]. Also, extreme cranial-facial asymmetry is often present, where the forehead is tilted as a consequence of frontal lobe hypoplasia, characteristic of severe cases and may even occur in babies without microcephaly [55].

Ophthalmic abnormalities: an investigation in Colombia and Venezuela found that CZS has a high incidence to cause severe optic nerve as well as macular defects (88%) also a substantial rate of anterior segment abnormalities (12%). Bilateral ocular involvement was universal in their study. Therefore, they recommend that an ophthalmic examination be performed in all patients with CZS [56].

The relationship between maternal infection during the first pregnancy and microcephaly generates a high-risk factor for the newborn to present ocular abnormalities. CZS differs from other congenital infections in chorioretinal atrophy, which is well defined and the macroscopic pigmentation, which generally affects the macular region, is unique in ZIKV infection [57].

The most commonly reported eye injuries include macular pigment spots and choriorethian atrophy that tend to be located in the posterior pole of the eye, especially in the macular area. Also, microphthalmia and coloboma, congenital cataracts, and intraocular calcifications have been reported [58]. Among other findings that have been reported in infants with CSZ are optic nerve involvement, including hypoplasia, optic nerve venting and atrophy, severe optic disc hollowing, lens subluxation and bilateral iris coloboma. Although the mothers of the infants maintained normal visual function during and after pregnancy [59].

The pathogenesis of posterior eye injuries is not known yet, however, it could be due to direct cell damage by ZIKV or inflammatory sequelae. Active chorioretinitis is a possible precursor to chorioretinal atrophy [60]. Likewise, blindness has been associated with expression of the Axl protein receptor found in retinal stem cells [61].

Brain abnormalities: the macroscopic brain pathology caused in CZS has a great similarity to the neuropathology related to congenital cytomegalovirus (CMV) [62]. Most evident difference is the distribution of intracranial calcifications, mostly subcortical in the grey-white junction in congenital ZIKV infection and periventricular in CMV [23].

Among the anomalies detected are the presence of diffuse calcifications in the subcortical area which can cause cell death, differentiating them from other congenital infections. Furthermore, there is an increase in ventricular and extra axial fluid spaces; cortical thinning with abnormalities in the convolutions; hypoplasia or absence of the corpus callosum; reduced myelin; and hypoplasia of the cerebellum or cerebellar vermis [63]. Also, calcifications have been evidenced in the basal ganglia and in the brain stem [64].

Brain abnormalities can be detected prenatally with ultrasound or MRI [65]. It is more complex in severe microcephaly because the anterior fontanel is tiny or closed, making transfontanellar ultrasound difficult in the newborn [66]. In this respect, in an evaluation of women infected with ZIKV, fetal ultrasound showed that 17% of the fetuses had calcifications or other CNS anomalies [23]. Subsequently, a study in which one-month old Rhesus monkeys (in humans, equivalent to three months of life) were infected with ZIVK showed that brain damage and behavioural alterations can be caused even when the infection has occurred after birth [67].

Congenital contractures: congenital contractures that have been reported occurring in one or more joints (arthrogryposis) on infants with CZS, are likely to develop in association with hypoplasia of the brainstem and thinning of the entire spinal cord [68]. Other factors that also influence in the etiology of anthrogryposis are uterine malformations, genetic disorders and maternal disorders [69]. Depending on the location of the contracture, whether it is lateral, in the upper or lower limb, its clinical presentation changes and in terms of severity it usually manifests itself with neurological deterioration [70].

Neurogenic factors affecting the corticospinal tract, motor neurons or their interactions can cause fetal motor abnormalities, leading to decreased fetal movement and contractures [71].

Motor impairments can also lead to other serious consequences. In addition to causing a delay in motor development, dyspraxia can also have implications for feeding (e.g. chewing and swallowing). Dysphagia has caused them to fail to develop their motor functions and many others have needed feeding tubes [72].

Neurological sequelae: information about the long-term development of children with CSZ is minimal. Most have had severe neurological sequelae and cognitive disabilities that vary depending on severity, in addition the complications associated with respiratory infections, dysphagia and reflux, epilepsy and hydrocephalus that could be fatal [73].

Neurological examination of infected newborns showed hypertonia and spasticity, irritability with excessive crying and hypotonia in a few cases [74]. According to records, other severe neurological manifestations include tremors and postures consistent with extrapyramidal dysfunction [75], encephalitis, meningoencephalitis, cerebellitis, acute disseminated encephalomyelitis, encephalopathies with epileptic seizures, inflammatory myelopathy and alterations of the cranial nerves [76].

Most CZS babies are expected to survive, even if they require ongoing medical care. Reports suggest that many of the children with CZS on their first birthday had a functioning of a 2 to 3 months old level [77]. Presenting functional disability and some level of intellectual disability,

most likely in the range of severe to profound. Lack or abnormal neuronal development, cerebral palsy, intellectual disability and epilepsy are strongly related to microcephaly [78].

As for language, the ability to understand and produce it is consistent with the level of intellectual disability. Comorbid hearing problems suggest difficulty in communication in children with CZS [79]. The production of speech is made more difficult by motor and cognitive deficiencies. Some children with CZS can understand verbal communication but not express themselves in words [80].

Infants with CZS are likely to have long-term social, emotional, and behavioral challenges. Facial distortions, severe hyperactivity and irritability, and an inability to calm down have been reported in infants with CZS [81]. Irritability can be caused by pain, difficulties in regulating sensory input, abnormal sleep patterns, frustrations with communication, and outpatient challenges during their growth [82].

They have a higher risk to present psychiatric disorders, although the severity of the intellectual disability is likely to make it harder to diagnose. Since children with CZS have multiple vulnerabilities, they may have limitations in their development of functional skills. Basic activities of daily living will be compromised, so most children with CZS will require lifelong care [83].

In addition, a clear connection has been established between ZIKV infection and Guillain-Bar syndrome (GBS) which is a rare disorder in which the body's immune system attacks the nerves [84]. This association was identified in French Polynesia and other regions that have a high rate of ZIKV morbidity [84,85].

In regard of the immune system, the organism fights the peripheral nervous system (PNS) after infection with ZIKV, causing an albuminocyte dissociation in the cerebrospinal fluid and a demyelination and inflammation of various nerve roots [86]. The symptoms that it causes are muscle weakness, numbness or pain in the fingers and toes, pain that spreads to the arms, walking problems, irritability, breathing problems and facial weakness. It may be a benign condition, but it can also cause death if the paralysis of the chest muscles is not treated, also leading to breathing problems [87].

Discussion

The epidemiological link between Zika and microcephaly was first reported in Brazil in 2015 [88]. Prior to this, cases of microcephaly were reported in French Polynesia in 2013; however, this was not significant because no concrete data was established to associate the virus with microcephaly, but it was possible to prove perinatal transmission of ZIKV. This data represents an important event, which will be related to the outbreak in Brazil 2015, where several patients with ZIKV symptomatology were investigated and it was concluded that this was the agent that originated the outbreak, and that it corresponded to an expansion of the Asian lineage [88].

Between the causes of microcephaly, three theories have been established about how the virus manages to infect the fetus, the most widely accepted is the entry of the virus through receptors, even coinciding with the study carried out [89] about the dependence of the receptor AXL responsible for infecting the fetal endothelial cells. This finding differentiates ZIKV from other flaviviruses such as Dengue (DENV) or West Nile virus (WNV). As such, it could be noted that ZIKV uses the AXL receptor as an entry cofactor into umbilical vein endothelial cells. The importance of this receptor is referred to in the study [61] as the possibility of blocking this receptor in a way of preventing viral replication, even though this would have negative consequences. Despite that, another report to develop antivirals that target the components needed by the virus to replicate, proposing the inhibition of AXL, however these do not eliminate the possibility of infection to glial cells [90].

One of the characteristics mentioned previously, agrees with a study of a sample from fetal tissue post mortem [67] in which a large amount of apoptosis was found affecting mainly the developing neurons migrating to the neocortex. That was associated with an early mineralization of them, however, the neurons differentiated in the germinal matrix, were not affected. Other authors mention that it specifically targets the process of neural cell formation, and that the already differentiated cells have their own defense mechanism that prevents them from being infected by ZIKV [91]. In general terms, the authors conclude that when ZIKV affects pregnant women, after crossing the placental barrier it is neurotrophic, affecting the neurons during their development.

As far as clinical manifestations are concerned, we agree that intrauterine ZIKV infection appears to be directly related to the appearance of congenital anomalies mainly cerebral anomalies causing birth defects including microcephaly, neural tube damage, ophthalmological abnormalities and other central nervous system disorders [92].

Apparently the most common period of infection is the late first trimester and early second trimester; however, it suggests that brain damage and behavioral disturbances may occur even when the infection has taken place after birth [93]. On the contrary, Martínes et al. [24] mentioned that there is only evidence for the first trimester, based on studies of placentas where viral antigens have been found in the chorionic villi.

Microcephaly is considered to be the main alteration in cranial morphology caused by CZV. This variation seems to be caused by modification of the neuronal cells. This statement coincides with the suggestion that demyelination of the white substance, and cerebellar hypoplasia in most infants, suggests that ZIKV is connected to the disruption of neural development by affecting neural and glial proliferation, as well as their migration [36].

However, it differs from the studies carried out by Roberts and Frosh [94], who indicate that there is destruction in the brain tissue such as calcifications, gliosis and necrosis, suggesting a process of cellular destruction, demonstrated by the continuous presence of the virus.

When it comes to brain abnormalities, the diffuse calcifications in the subcortical area, which can cause cell death, are different from other congenital infections. In this regard, in a postmortem study of seven neonates with congenital ZIKV infection, macroscopic and microscopic calcifications were found in three patterns: individual neuronal mineralization, a fine granular pattern and coarse banded calcification [95]. However, the lymphocytic choriomeningitis virus also shows a strong tropism towards the neuroblasts, causing periventricular calcifications, cortical dysplasia and focal brain destruction [96].

Unfortunately, the specific mechanism that develops contractures with CZS is uncertain. Neurogenic factors affecting the corticospinal tract, motor neurons or their interactions are considered likely to cause motor abnormalities, causing fetal movements and contractures to be reduced. Arthrogryposis was connected to ZIKV for the damage it causes to central and peripheral motor neurons, but not to the abnormalities of the joints themselves [68]. However, other authors consider that it may be due to a physical limitation of intrauterine movement, maternal disorders and genetic alterations and therefore ZIKV should not be established as the definitive cause [97].

Information about the long-term development of children with CSZ is minimal. Most have had severe neurological sequelae and cognitive disabilities [75]. For Cao-Lormeau et al. [98] there is a clear association between ZIKV infection in infants and Guillain-Barré syndrome.

Conclusion

There is a direct relationship between the appearance of microcephaly together with ZIKV. The studies carried out on the two main outbreaks in French Polynesia and Brazil, show pieces of evidence that, when gathered together, are sufficient support. Since alterations in the newborn arise when ZIKV enters the placenta, through receptors including AXL, and this manages to reach the fetus, with a greater predilection towards the hippocampus and cerebral cortex, affecting the developing neurogerm cells, therefore, the consequences are more drastic when the pregnant woman is infected during the first trimester of pregnancy.

The virus, not only causes microcephaly, but also other neurological anomalies. This is mainly caused by the way it enters the fetus and attacks the cells, preventing their development and differentiation, thereby affecting their functioning.

Conflict of Relationships and Activities

The authors declare that they do not present conflicts of relationships and activities during the development of this research.

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Bibliographic References

1. Torres AH, Vázquez EG, Escudero EM, Martínez JAH, Gómez JG, Hernández MS. Infecciones víricas endémicas: dengue, fiebre del Nilo y otras viriasis. Med - Programa Form Médica Contin Acreditado [Internet]. 2018;12(57):3337-48. Available from: https://www.sciencedirect.com/science/article/pii/S0304541218301318 DOI: 10.1016/j.med.2018.05.001 Dialnet Google Scholar Microsoft Academic

2. OPS/OMS. Alerta Epidemiológica: Infección por virus Zika 7 de mayo de 2015 [Internet]. Washington, D.C. 2015 [cited January 8 2020]. Available from: https://www.paho.org/hq/index.php?option=com_content&view=article&id=10899:2015-7-may-2015-zika-virus-infection&Itemid=42346&lang=es

3. Ledermann JP, Guillaumot L, Yug L, Saweyog SC, Tided M, Machieng P, et al. *Aedes hensilli* as a Potential Vector of Chikungunya and Zika Viruses. PLoS Negl Trop Dis [Internet]. October 9 2014;8(10):e3188. Available from: https://journals.plos.org/plosntds/article?id=10.1371/journal.pntd.0003188 DOI: 10.1371/journal.pntd.0003188 PMID 25299181 PMCID PMC4191940 Google Scholar Microsoft Academic

4. Cabrera-Gaytán DA, Galván-Hernández SA. Manifestaciones clínicas del Virus Zika. Rev Med Inst Mex Seguro Soc [Internet]. May 15 2016;54(2):225-9. Available from: https://www.medigraphic.com/cgi-bin/new/resumen.cgi?IDARTICULO=65217 PMID 26960051 Redalyc Google Scholar Microsoft Academic

5. Haddow AD, Schuh AJ, Yasuda CY, Kasper MR, Heang V, Huy R, et al. Genetic Characterization of Zika Virus Strains: Geographic Expansion of the Asian Lineage. PLoS Negl Trop Dis [Internet]. February 28 2012;6(2):e1477. Available from: https://journals.plos.org/plosntds/article?id=10.1371/journal.pntd.0001477 DOI: 10.1371/journal.pntd.0001477 PMID 22389730 PMCID: PMC3289602 Google Scholar Microsoft Academic

6. Klase ZA, Khakhina S, Schneider ADB, Callahan M V, Glasspool-Malone J, Malone R. Zika Fetal Neuropathogenesis: Etiology of a Viral Syndrome. PLoS Negl Trop Dis [Internet]. August 25 2016;10(8):e0004877. Available from: https://doi.org/10.1371/journal.pntd.0004877 DOI: 10.1371/journal.pntd.0004877 PMID 27560129 PMCID PMC4999274 Google Scholar Microsoft Academic

7. Hennessey M, Fischer M, Staples JE. Zika Virus Spreads to New Areas-Region of the Americas, May 2015 - January 2016. MMWR Morb Mortal Wkly Rep 2016;65(3):55–58. Available from: https://www.cdc.gov/mmwr/volumes/65/wr/mm6503e1.htm DOI: 10.15585/mmwr.mm6503e1external icon PMID 26820163 Google Scholar Microsoft Academic

8. González Collantes SG. Situación epidemiológica del virus zika. An Fac Med [Internet]. May 16 2017;78(1):73-8. Available from: https://revistasinvestigacion.unmsm.edu.pe/index.php/anales/article/view/13025 DOI: 10.15381/anales.v78i1.13025 SciELO Redalyc Dialnet Google Scholar Microsoft Academic

9. Marcondes CB, Ximenes M de FF de M. Zika virus in Brazil and the danger of infestation by *Aedes* (*Stegomyia*) mosquitoes. Rev Soc Bras Med Trop [Internet]. 2016;49(1):4-10. Available from: https://www.scielo.br/scielo.php?script=sci_arttext&pid=S0037-86822015005003102&lng=en&nrm=iso&tlng=en DOI: 10.1590/0037-8682-0220-2015 PMID 26689277 SciELO Lilacs Google Scholar Microsoft Academic

10. Maguiña Vargas C. Zika, la nueva enfermedad emergente en América. Rev Medica Hered [Internet]. 2016;27(1):3-6. Available from: http://revistas.upch.edu.pe/index.php/RMH/article/download/2776/2639 SciELO Lilacs Redalyc Google Scholar Microsoft Academic

11. Maguiña C, Galán-Rodas E. El virus Zika: una revisión de literatura. Acta Médica Peru [Internet]. May 16 2016;33(1):34-41. Available from: https://amp.cmp.org.pe/index.php/AMP/article/view/16 DOI: 10.35663/amp.2016.331.16 SciELO Lilac Redalyc Google Scholar Microsoft Academic

12. Schaub B, Gueneret M, Jolivet E, Decatrelle V, Yazza S, Gueye H, et al. Ultrasound imaging for identification of cerebral damage in congenital Zika virus syndrome: a case series. Lancet Child Adolesc Heal [Internet]. September 1 2017;1(1):45-55. Available from: https://doi.org/10.1016/S2352-4642(17)30001-9 DOI: 10.1016/S2352-4642(17)30001-9 PMID 30169227 Google Scholar Microsoft Academic

13. Ministerio de Salud Pública del Ecuador. Respuesta frente al virus Zika en el Ecuador [Internet]. 2016 [Cited january 8 2020]. Available from: https://www.salud.gob.ec/wp-content/uploads/2015/12/RESPUESTA-FRENTE-AL-ZIKA.pdf

14. Chavali PL, Stojic L, Meredith LW, Joseph N, Nahorski MS, Sanford TJ, et al. Neurodevelopmental protein Musashi-1 interacts with the Zika genome and promotes viral replication. Science [Internet]. July 7 2017;357(6346):83-8. Available from: http://science.sciencemag.org/content/357/6346/83.abstract DOI: 10.1126/science.aam9243 PMID 28572454 PMCID PMC5798584 Google Scholar Microsoft Academic

15. Gascon-Jimenez FJ, Gallardo-Hernandez FL, Fernandez-Ramos JA, Aguilar-Quintero M, Camino-Leon R, Lopez-Laso E. Microcefalia primaria hereditaria de tipo 5. No todo es virus del Zika. Rev Neurol [Internet]. February 2018;66(3):101-2. Available from: https://www.neurologia.com/articulo/2017301 DOI: 10.33588/rn.6603.2017301 PMID 29368329 Lilacs Dialnet Google Scholar Microsoft Academic

16. Weatherhead JE, da Silva J, Murray KO. Threat of Zika Virus to the 2016 Rio de Janeiro Olympic and Paralympic Games. Curr Trop Med Reports [Internet]. 2016;3(3):120-5. Disponible en: https://doi.org/10.1007/s40475-016-0076-0 DOI: 10.1007/s40475-016-0076-0 Google Scholar Microsoft Academic

17. Rivadeneyra-Espinar PG, Venegas-Esquivel GA, Díaz-Espinoza CM, Pérez-Robles VM, González-Fernández MI, Sesma-Medrano E. Zika como causa de aborto espontáneo en zonas endémicas. Bol Med Hosp Infant Mex [Internet]. June 13 2019;76(4):193-7. Available from: https://www.bmhim.com/frame_esp.php?id=87# DOI: 10.24875/bmhim.19000116 PMID 31303651 SciELO Lilacs Google Scholar Microsoft Academic

18. Albinagorta Olórtegui R, Díaz Vela M del P. Salud fetal y diagnóstico ultrasonográfico en la infección perinatal por el virus zika. Rev Peru Ginecol y Obstet [Internet]. April 22 2017;63(1):71-9. Available from: http://spog.org.pe/web/revista/index.php/RPGO/article/view/1968 DOI: 10.31403/rpgo.v63i1968 SciELO Lilac Redalyc Dialnet Google Scholar Microsoft Academic

19. Arroyo HA. Microcefalia. Med (Buenos Aires) [Internet]. 2018;78(2):94-100. Available from: https://www.medicinabuenosaires.com/PMID/30199373.pdf PMID 30199373 Lilacs Google Scholar

20. de Oliveira WK, de França GVA, Carmo EH, Duncan BB, de Souza Kuchenbecker R, Schmidt MI. Infection-related microcephaly after the 2015 and 2016 Zika virus outbreaks in Brazil: a surveillance-based analysis. Lancet [Internet]. August 26 2017;390(10097):861-70. Available from: https://doi.org/10.1016/S0140-6736(17)31368-5 DOI: 10.1016/S0140-6736(17)31368-5 PMID 28647172 Google Scholar Microsoft Academic

21. Moraes M, Sobrero H, Mayans E, Borbonet D. Infección por virus Zika en el embarazo y el recién nacido. Arch Pediatr Urug. 2016;87(4):374-83. Available from: https://www.sup.org.uy/archivos-de-pediatria/adp87-4/web/pdf/adp87-4_pauta%20zika.pdf SciELO Google Scholar Microsoft Academic

22. de Oliveira CS, da Costa Vasconcelos PF. Microcephaly and Zika virus. J Pediatr (Rio J) [Internet]. 2016;92(2):103-5. Available from: https://www.sciencedirect.com/science/article/pii/S0021755716000395 DOI: 10.1016/j.jped.2016.02.003 PMID 27036749 SciELO Lilacs Google Scholar Microsoft Academic

23. Brasil P, Pereira JP, Moreira ME, Ribeiro Nogueira RM, Damasceno L, Wakimoto M, et al. Zika Virus Infection in Pregnant Women in Rio de Janeiro. N Engl J Med [Internet]. March 4 2016;375(24):2321-34. Available from: https://doi.org/10.1056/NEJMoa1602412 DOI: 10.1056/NEJMoa1602412 PMID 26943629 PMCID PMC5323261 Google Scholar Microsoft Academic

24. Martines RB, Bhatnagar J, de Oliveira Ramos AM, Davi HPF, Iglezias SD, Kanamura CT, et al. Pathology of congenital Zika syndrome in Brazil: a case series. Lancet [Internet]. August 27 2016;388(10047):898-904. Available from: https://doi.org/10.1016/S0140-6736(16)30883-2 DOI: 10.1016/S0140-6736(16)30883-2 PMID 27372395 Google Scholar Microsoft Academic

25. Shapiro-Mendoza CK, Rice ME, Galang RR, Fulton AC, VanMaldeghem K, Prado MV, et al. Pregnancy Outcomes After Maternal Zika Virus Infection During Pregnancy - U.S. Territories, January 1, 2016-April 25, 2017. MMWR Morb Mortal Wkly Rep [Internet]. June 2017;66(23):615-21. Available from: https://www.cdc.gov/mmwr/volumes/66/wr/mm6623e1.htm DOI: 10.15585/mmwr.mm6623e1 PMID 28617773 PMCID PMC5657842 Google Scholar Microsoft Academic

26. World Health Oranization. Zika Virus IHR Emergency Committee [Internet]. [Cited january 8 2020]. Available from: https://www.who.int/groups/zika-virus-ihr-emergency-committee

27. Mlakar J, Korva M, Tul N, Popović M, Poljšak-Prijatelj M, Mraz J, et al. Zika Virus Associated with Microcephaly. N Engl J Med [Internet]. February 10 2016;374(10):951-8. Available from: https://doi.org/10.1056/NEJMoa1600651 DOI: 10.1056/NEJMoa1600651 PMID 26862926 Google Scholar Microsoft Academic

28. Wen Z, Song H, Ming GL. How does Zika virus cause microcephaly? [Internet]. Genes and Development. 2017;31(9):849-61. Available from: http://genesdev.cshlp.org/content/31/9/849.long DOI: 10.1101/gad.298216.117 PMID 28566536 PMCID PMC5458753 Google Scholar Microsoft Academic

29. Adiga R. Phylogenetic analysis of the NS5 gene of Zika virus. J Med Virol [Internet]. October 1 2016;88(10):1821-6. Available from: https://doi.org/10.1002/jmv.24615 DOI: 10.1002/jmv.24615 PMID 27335310 Google Scholar Microsoft Academic

30. Hamel R, Dejarnac O, Wichit S, Ekchariyawat P, Neyret A, Luplertlop N, et al. Biology of Zika Virus Infection in Human Skin Cells. J Virol [Internet]. September 1 2015;89(17):8880-96. Available from: http://jvi.asm.org/content/89/17/8880.abstract DOI: 10.1128/JVI.00354-15 PMID 26085147 PMCID PMC4524089 Google Scholar Microsoft Academic

31. Raghunath P. Does Zika Virus Really Causes Microcephaly in Children Whose Mothers Became Infected with the Virus during Their Pregnancy? Iran J Public Health [Internet]. April 2018;47(4):613-4. Available from: http://ijph.tums.ac.ir/index.php/ijph/article/view/13168/5964 PMID 29900151 Google Scholar Microsoft Academic

32. Hanners NW, Eitson JL, Usui N, Richardson RB, Wexler EM, Konopka G, et al. Western Zika Virus in Human Fetal Neural Progenitors Persists Long Term with Partial Cytopathic and Limited Immunogenic Effects. Cell Rep [Internet]. June 14 2016;15(11):2315-22. Available from: https://doi.org/10.1016/j.celrep.2016.05.075 DOI: 10.1016/j.celrep.2016.05.075 PMID 27268504 PMCID PMC5645151 Google Scholar Microsoft Academic

33. Cavalheiro S, Lopez A, Serra S, Da Cunha A, da Costa MDS, Moron A, et al. Microcephaly and Zika virus: neonatal neuroradiological aspects. Child's Nerv Syst [Internet]. 2016;32(6):1057-60. Available from: https://doi.org/10.1007/s00381-016-3074-6 DOI: 10.1007/s00381-016-3074-6 PMID 27080092 PMCID PMC4882355 Google Scholar Microsoft Academic

34. Adibi JJ, Marques Jr ETA, Cartus A, Beigi RH. Teratogenic effects of the Zika virus and the role of the placenta. Lancet [Internet]. April 9 2016;387(10027):1587-90. Available from: https://doi.org/10.1016/S0140-6736(16)00650-4 DOI: 10.1016/S0140-6736(16)00650-4 PMID 26952548 Google Scholar Microsoft Academic

35. Coronell-Rodríguez W, Arteta-Acosta C, Suárez-Fuentes MA, Burgos-Rolon MC, Rubio-Sotomayor MT, Sarmiento-Gutiérrez M, et al. Infección por virus del Zika en el embarazo, impacto fetal y neonatal. Rev Chil Infect [Internet]. 2016;33(6):665-73. Available from: https://scielo.conicyt.cl/scielo.php?pid=S0716-10182016000600009&script=sci_arttext&tlng=n DOI: 10.4067/S0716-10182016000600009 PMID 28146192 SciELO Lilacs Google Scholar Microsoft Academic

36. Li C, Xu D, Ye Q, Hong S, Jiang Y, Liu X, et al. Zika Virus Disrupts Neural Progenitor Development and Leads to Microcephaly in Mice. Cell Stem Cell [Internet]. July 7 2016;19(1):120-6. Available from: https://doi.org/10.1016/j.stem.2016.04.017 DOI: 10.1016/j.stem.2016.10.017 PMID 27179424 Google Scholar Microsoft Academic

37. Aspilcueta-Gho D, Benites Villafane C, Calderón Sánchez MM, Calderón Yberico JG. Infección por zika en el Perú: de amenaza a problema de salud. Rev Peru Ginecol y Obstet [Internet]. 2017;63(1):57-64. Available from: http://www.spog.org.pe/web/revista/index.php/RPGO/article/view/1965 DOI: 10.31403/rpgo.v63i1965 SciELO Lilacs Redalyc Dialnet Google Scholar Microsoft Academic

38. Cugola FR, Fernandes IR, Russo FB, Freitas BC, Dias JLM, Guimarães KP, et al. The Brazilian Zika virus strain causes birth defects in experimental models. Nature [Internet]. 2016;534(7606):267-71. Available from: https://doi.org/10.1038/nature18296 DOI: 10.1038/nature18296 PMID 27279226 PMCID PMC4902174 Google Scholar Microsoft Academic

39. Retallack H, Di Lullo E, Arias C, Knopp KA, Laurie MT, Sandoval-Espinosa C, et al. Zika virus cell tropism in the developing human brain and inhibition by azithromycin. Proc Natl Acad Sci [Internet]. December 13 2016;113(50):14408-14413. Available from: http://www.pnas.org/content/113/50/14408.abstract DOI: 10.1073/pnas.1618029113 PMID 27911847 PMCID: PMC5167169 Google Scholar Microsoft Academic

40. Calvet G, Aguiar RS, Melo ASO, Sampaio SA, de Filippis I, Fabri A, et al. Detection and sequencing of Zika virus from amniotic fluid of fetuses with microcephaly in Brazil: a case study. Lancet Infect Dis [Internet]. June 1 2016;16(6):653-60. Available from: https://doi.org/10.1016/S1473-3099(16)00095-5 DOI: 10.1016/S1473-3099(16)00095-5 PMID 26897108 Google Scholar Microsoft Academic

41. Miner JJ, Diamond MS. Zika Virus Pathogenesis and Tissue Tropism. Cell Host Microbe [Internet]. February 8 2017;21(2):134-42. Available from: https://doi.org/10.1016/j.chom.2017.01.004 DOI: 10.1016/j.chom.2017.01.004 PMID 28182948 PMCID PMC5328190 Google Scholar Microsoft Academic

42. Xie X, Shan C, Shi P-Y. Restriction of Zika Virus by Host Innate Immunity. Cell Host Microbe [Internet]. May 11 2016;19(5):566-7. Available from: https://doi.org/10.1016/j.chom.2016.04.019 DOI: 10.1016/j.chom.2016.04.019 PMID 27173920 Google Scholar Microsoft Academic

43. Bayer A, Lennemann NJ, Ouyang Y, Bramley JC, Morosky S, Marques Jr. ETDA, et al. Type III Interferons Produced by Human Placental Trophoblasts Confer Protection against Zika Virus Infection. Cell Host Microbe [Internet]. 11 de mayo de 2016;19(5):705-12. Available from: https://doi.org/10.1016/j.chom.2016.03.008 DOI: 10.1016/j.chom.2016.03.008 PMID 27066743 PMCID PMC4866896 Google Scholar Microsoft Academic

44. Adibi JJ, Zhao Y, Cartus AR, Gupta P, Davidson LA. Placental Mechanics in the Zika-Microcephaly Relationship. Cell Host Microbe [Internet]. July 13 2016;20(1):9-11. Available from: https://doi.org/10.1016/j.chom.2016.06.013 DOI: 10.1016/j.chom.2016.06.013 PMID 27414496 Google Scholar Microsoft Academic

45. Lazear HM, Diamond MS. Zika Virus: New Clinical Syndromes and Its Emergence in the Western Hemisphere. J Virol [Internet]. May 15 2016;90(10):4864-4875. Available from: http://jvi.asm.org/content/90/10/4864.abstract DOI:

10.1128/JVI.00252-16 PMID 26962217 PMCID PMC4859708 Google Scholar Microsoft Academic

46. Russo FB, Jungmann P, Beltrão-Braga PCB. Zika infection and the development of neurological defects. Cell Microbiol [Internet]. June 1 2017;19(6):e12744. Available from: https://doi.org/10.1111/cmi.12744 DOI: 10.1111/cmi.12744 PMID 28370966 Google Scholar Microsoft Academic

47. Liang Q, Luo Z, Zeng J, Chen W, Foo S-S, Lee S-A, 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 [Internet]. 2016;19(5):663-71. Available from: https://www.sciencedirect.com/science/article/pii/S1934590916302144 DOI: 10.1016/j.stem.2016.07.019 PMID 27524440 PMCID PMC5144538 Google Scholar Microsoft Academic

48. Lugones Botell M, Ramírez Bermúdez M. Infección por virus zika en el embarazo y microcefalia. Rev Cuba Obstet y Ginecol [Internet]. 2016;42(3):398-411. Available from: http://www.revginecobstetricia.sld.cu/index.php/gin/article/view/83 SciELO Lilacs Google Scholar Microsoft Academic

49. Sarno M, Aquino M, Pimentel K, Cabral R, Costa G, Bastos F, et al. Progressive lesions of central nervous system in microcephalic fetuses with suspected congenital Zika virus syndrome. Ultrasound Obstet Gynecol [Internet]. Decembre 1 2017;50(6):717-22. Available from: https://doi.org/10.1002/uog.17303 DOI: 10.1002/uog.17303 PMID 27644020 Google Scholar Microsoft Academic

50. Oliveira Melo AS, Malinger G, Ximenes R, Szejnfeld PO, Alves Sampaio S, Bispo de Filippis AM. Zika virus intrauterine infection causes fetal brain abnormality and microcephaly: tip of the iceberg? Ultrasound Obstet Gynecol [Internet]. January 1 2016;47(1):6-7. Available from: https://doi.org/10.1002/uog.15831 DOI: https://doi.org/10.1002/uog.15831 PMID 26731034 Google Scholar Microsoft Academic

51. Qian X, Nguyen HN, Song MM, Hadiono C, Ogden SC, Hammack C, et al. Brain-Region-Specific Organoids Using Mini-bioreactors for Modeling ZIKV Exposure. Cell [Internet]. May 19 2016;165(5):1238-54. Available from: https://doi.org/10.1016/j.cell.2016.04.032 DOI: 10.1016/j.cell.2016.04.032 PMID 27118425 PMCID PMC4900885 Google Scholar Microsoft Academic

52. Satterfield-Nash A, Kotzky K, Allen J, Bertolli J, Moore CA, Pereira IO, et al. Health and Development at Age 19-24 Months of 19 Children Who Were Born with Microcephaly and Laboratory Evidence of Congenital Zika Virus Infection During the 2015 Zika Virus Outbreak - Brazil, 2017. MMWR Morb Mortal Wkly Rep [Internet]. December 2017;66(49):1347-51. Available from: https://www.cdc.gov/mmwr/volumes/66/wr/mm6649a2.htm DOI: 10.15585/mmwr.mm6649a2 PMID 29240727 PMCID PMC5730218 Google Scholar Microsoft Academic

53. Yale School of Medicine. Findings Shed New Light On Why Zika Causes Birth Defects In Some Pregnancies [Internet]. 2019 [Cited November 15 2019]. Available from: https://medicine.yale.edu/news-article/21037/

54. Parmar H, Ibrahim M. Pediatric Intracranial Infections. Neuroimaging Clin N Am [Internet]. 2012;22(4):707-25. Available from: https://www.sciencedirect.com/science/article/pii/S1052514912000846 DOI: 10.1016/j.nic.2012.05.016 PMID 23122263 Google Scholar Microsoft Academic

55. van der Linden V, Pessoa A, Dobyns W, Barkovich AJ, van der Linder H, Rolim EL, et al. Description of 13 Infants Born During October 2015-January 2016 With Congenital Zika Virus Infection Without Microcephaly at Birth-Brazil. MMWR Morb Mortal Wkly Rep [Internet]. December 2016;65(47):1343-8. Available from: https://www.cdc.gov/mmwr/volumes/65/wr/mm6547e2.htm DOI: 10.15585/mmwr.mm6547e2 PMID 27906905 Google Scholar Microsoft Academic

56. Yepez JB, Murati FA, Pettito M, Peñaranda CF, de Yepez J, Maestre G, et al. Ophthalmic Manifestations of Congenital Zika Syndrome in Colombia and Venezuela. JAMA Ophthalmol [Internet]. May 1 2017;135(5):440-5. Available from: https://doi.org/10.1001/jamaophthalmol.2017.0561 DOI: 10.1001/jamaophthalmol.2017.0561 PMID 28418539 PMCID PMC5470423 Google Scholar Microsoft Academic

57. Ventura C V, Maia M, Travassos SB, Martins TT, Patriota F, Nunes ME, et al. Risk Factors Associated With the Ophthalmoscopic Findings Identified in Infants With Presumed Zika Virus Congenital Infection. JAMA Ophthalmol [Internet]. August 1 2016;134(8):912-8. Available from: https://doi.org/10.1001/jamaophthalmol.2016.1784 DOI: 10.1001/jamaophthalmol.2016.1784 PMID 27228275 Google Scholar Microsoft Academic

58. Roach T, Alcendor DJ. Zika virus infection of cellular components of the blood-retinal barriers: implications for viral associated congenital ocular disease. J Neuroinflammation [Internet]. 2017;14(1):43. Available from: https://doi.org/10.1186/s12974-017-0824-7 DOI: 10.1186/s12974-017-0824-7 PMID 28253931 PMCID PMC5335843 Google Scholar Microsoft Academic

59. Ventura C V, Maia M, Ventura B V, Linden V Van Der, Araújo EB, Ramos RC, et al. Ophthalmological findings in infants with microcephaly and presumable intra-uterus Zika virus infection. Arq Bras Oftalmol [Internet]. 2016;79(1):1-3. Available from: https://www.scielo.br/scielo.php?script=sci_arttext&pid=S0004-27492016000100002&lng=en&nrm=iso&tlng=en PMID 26840156 SciELO Lilacs Google Scholar Microsoft Academic

60. de Paula Freitas B, de Oliveira Dias JR, Prazeres J, Sacramento GA, Ko AI, Maia M, et al. Ocular Findings in Infants With Microcephaly Associated With Presumed Zika Virus Congenital Infection in Salvador, Brazil. JAMA Ophthalmol [Internet]. May 1 2016;134(5):529-35. Available from: https://doi.org/10.1001/jamaophthalmol.2016.0267 DOI: 10.1001/jamaophthalmol.2016.0267 PMID 26865554 PMCID PMC5444996 Google Scholar Microsoft Academic

61. Nowakowski TJ, Pollen AA, Di Lullo E, Sandoval-Espinosa C, Bershteyn M, Kriegstein AR. Expression Analysis Highlights AXL as a Candidate Zika Virus Entry Receptor in Neural Stem Cells. Cell Stem Cell [Internet]. 2016;18(5):591-6. Available from: https://www.sciencedirect.com/science/article/pii/S1934590916001181 DOI: 10.1016/j.stem.2016.03.012 PMID 27038591 PMCID PMC4860115 Google Scholar Microsoft Academic

62. Averill LW, Kandula VVR, Akyol Y, Epelman M. Fetal Brain Magnetic Resonance Imaging Findings In Congenital Cytomegalovirus Infection With Postnatal Imaging Correlation. Semin Ultrasound, CT MRI [Internet]. 2015;36(6):476-86. Available from: https://www.sciencedirect.com/science/article/pii/S0887217115000244 DOI: 10.1053/j.sult.2015.04.001 PMID 26614131 Google Scholar Microsoft Academic

63. Microcephaly Epidemic Research Group. Microcephaly in Infants, Pernambuco State, Brazil, 2015. Emerg Infect Dis [Internet]. June 2016;22(6):1090-3. Available from: https://wwwnc.cdc.gov/eid/article/22/6/16-0062_article DOI: 10.3201/eid2206.160062 PMID 27071041 PMCID PMC4880105 Google Scholar

64. Soares de Oliveira-Szejnfeld P, Levine D, Melo AS de O, Amorim MMR, Batista AGM, Chimelli L, et al. Congenital Brain Abnormalities and Zika Virus: What the Radiologist Can Expect to See Prenatally and Postnatally. Radiology [Internet]. August 23 2016;281(1):203-18. Available from: https://doi.org/10.1148/radiol.2016161584 DOI: 10.1148/radiol.2016161584 PMID 27552432 Google Scholar Microsoft Academic

65. Werner H, Fazecas T, Guedes B, Lopes Dos Santos J, Daltro P, Tonni G, et al. Intrauterine Zika virus infection and microcephaly: correlation of perinatal imaging and three-dimensional virtual physical models. Ultrasound Obstet Gynecol [Internet]. May 1 2016;47(5):657-60. Available from: https://doi.org/10.1002/uog.15901 DOI: 10.1002/uog.15901 PMID 26923098 Google Scholar Microsoft Academic

66. Driggers RW, Ho C-Y, Korhonen EM, Kuivanen S, Jääskeläinen AJ, Smura T, et al. Zika Virus Infection with Prolonged Maternal Viremia and Fetal Brain Abnormalities. N Engl J Med [Internet]. March 30 2016;374(22):2142-51. Available from: https://doi.org/10.1056/NEJMoa1601824 DOI: 10.1056/NEJMoa1601824 PMID 27028667 Google Scholar Microsoft Academic

67. Perez S, Tato R, Cabrera JJ, Lopez A, Robles O, Paz E, et al. Confirmed case of Zika virus congenital infection, Spain, March 2016. Eurosurveillance [Internet]. 2016;21(24). Available from: https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2016.21.24.30261 DOI: 10.2807/1560-7917.ES.2016.21.24.30261 PMID 27336620 Google Scholar Microsoft Academic

68. Aragao MFVV, Brainer-Lima AM, Holanda AC, van der Linden V, Vasco Aragão L, Silva Júnior MLM, et al. Spectrum of Spinal Cord, Spinal Root, and Brain MRI Abnormalities in Congenital Zika Syndrome with and without Arthrogryposis. Am J Neuroradiol [Internet]. May 1 2017;38(5):1045-53. Available from: http://www.ajnr.org/content/38/5/1045.abstract DOI: 10.3174/ajnr.A5125 PMID 28364011 Google Scholar Microsoft Academic

69. Garcez PP, Loiola EC, Madeiro da Costa R, Higa LM, Trindade P, Delvecchio R, et al. Zika virus impairs growth in human neurospheres and brain organoids. Science [Internet]. May 13 2016;352(6287):816-8. Available from: http://science.sciencemag.org/content/352/6287/816.abstract DOI: 10.1126/science.aaf6116 PMID 27064148 Google Scholar Microsoft Academic

70. van der Linden V, Rolim EL, Lins OG, van der Linden A, Aragão M de FVV, Brainer-Lima AM, et al. Congenital Zika syndrome with arthrogryposis: retrospective case series study. BMJ [Internet]. August 9 2016;354:i3899. Available from: http://www.bmj.com/content/354/bmj.i3899.abstract DOI: 10.1136/bmj.i3899 PMID 27509902 PMCID PMC4979356 Google Scholar Microsoft Academic

71. Kowalczyk B, Feluś J. Arthrogryposis: an update on clinical aspects, etiology, and treatment strategies. Arch Med Sci [Internet]. February 2016;12(1):10-24. Available from: https://www.archivesofmedicalscience.com/Arthrogryposis-an-update-on-clinical-aspects-etiology-and-treatment-strategies,53383,0,2.html DOI: 10.5114/aoms.2016.57578 PMID 26925114 PMCID PMC4754365 Google Scholar Microsoft Academic

72. Moura da Silva AA, Ganz JSS, Sousa P da S, Doriqui MJR, Ribeiro MRC, Branco MDRFC, et al. Early Growth and Neurologic Outcomes of Infants with Probable Congenital Zika Virus Syndrome. Emerg Infect Dis [Internet]. November 2016;22(11):1953-6. Available from: https://wwwnc.cdc.gov/eid/article/22/11/16-0956_article DOI: 10.3201/eid2211.160956 PMID 27767931 PMCID PMC5088045 Google Scholar Microsoft Academic

73. França GVA, Schuler-Faccini L, Oliveira WK, Henriques CMP, Carmo EH, Pedi VD, et al. Congenital Zika virus syndrome in Brazil: a case series of the first 1501 livebirths with complete investigation. Lancet [Internet]. August 27 2016;388(10047):891-7. Available from: https://doi.org/10.1016/S0140-6736(16)30902-3 DOI: 10.1016/S0140-6736(16)30902-3 PMID 27372398 Google Scholar Microsoft Academic

74. Carteaux G, Maquart M, Bedet A, Contou D, Brugières P, Fourati S, et al. Zika Virus Associated with Meningoencephalitis. N Engl J Med [Internet]. March 9 2016;374(16):1595-6. Available from: https://doi.org/10.1056/NEJMc1602964 DOI: 10.1056/NEJMc1602964 PMID 26958738 Google Scholar Microsoft Academic

75. Mulkey SB, Bulas DI, Vezina G, Fourzali Y, Morales A, Arroyave-Wessel M, et al. Sequential Neuroimaging of the Fetus and Newborn With In Utero Zika Virus Exposure. JAMA Pediatr [Internet]. January 1 2019;173(1):52-9. Available from: https://doi.org/10.1001/jamapediatrics.2018.4138 DOI: 10.1001/jamapediatrics.2018.4138 PMID 30476967 PMCID PMC6583436 Google Scholar Microsoft Academic

76. Soares CN, Brasil P, Carrera RM, Sequeira P, de Filippis AB, Borges VA, et al. Fatal encephalitis associated with Zika virus infection in an adult. J Clin Virol [Internet]. 2016;83:63-5. Available from: https://www.sciencedirect.com/science/article/pii/S1386653216305133 DOI: 10.1016/j.jcv.2016.08.297 PMID 27598870 Google Scholar Microsoft Academic

77. del Campo M, Feitosa IML, Ribeiro EM, Horovitz DDG, Pessoa ALS, França GVA, et al. The phenotypic spectrum of congenital Zika syndrome. Am J Med Genet Part A [Internet]. April 1 2017;173(4):841-57. Available from: https://doi.org/10.1002/ajmg.a.38170 DOI: 10.1002/ajmg.a.38170 PMID 28328129 Google Scholar Microsoft Academic

78. Chu A, Heald-Sargent T, Hageman JR. Primer on Microcephaly. Neoreviews [Internet]. January 1 2017;18(1):e44-e51. Available from: http://neoreviews.aappublications.org/content/18/1/e44.abstract DOI: 10.1542/neo.18-1-e44 Microsoft Academic

79. Leal MC, Muniz LF, Ferreira TSA, Santos CM, Almeida LC, Van Der Linden V, 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 [Internet]. September 2016;65(34):917-9. Available from: https://www.cdc.gov/mmwr/volumes/65/wr/mm6534e3.htm DOI: 10.15585/mmwr.mm6534e3 PMID 27585248 Google Scholar Microsoft Academic

80. Houwen S, Visser L, van der Putten A, Vlaskamp C. The interrelationships between motor, cognitive, and language development in children with and without intellectual and

developmental disabilities. Res Dev Disabil [Internet]. 2016;53-54:19-31. Available from: https://www.sciencedirect.com/science/article/pii/S0891422216300129 DOI: 10.1016/j.ridd.2016.01.012 PMID 26851384 Google Scholar Microsoft Academic

81. Moron AF, Cavalheiro S, Milani HJF, Sarmento SGP, Tanuri C, de Souza FF, et al. Microcephaly associated with maternal Zika virus infection. BJOG An Int J Obstet Gynaecol [Internet]. July 1 2016;123(8):1265-9. Available from: https://doi.org/10.1111/1471-0528.14072 DOI: 10.1111/1471-0528.14072 PMID 27150580 Google Scholar Microsoft Academic

82. Carvalho MDCG, Miranda-Filho D de B, van der Linden V, Sobral PF, Ramos RCF, Rocha MÂW, et al. Sleep EEG patterns in infants with congenital Zika virus syndrome. Clin Neurophysiol [Internet]. 2017;128(1):204-14. Available from: https://www.sciencedirect.com/science/article/pii/S1388245716306484 DOI: 10.1016/j.clinph.2016.11.004 PMID 27923187 Google Scholar Microsoft Academic

83. Wheeler AC. Development of Infants With Congenital Zika Syndrome: What Do We Know and What Can We Expect? Pediatrics [Internet]. February 1 2018;141(Supplement 2):S154-S160. Available from: http://pediatrics.aappublications.org/content/141/Supplement_2/S154.abstract DOI: 10.1542/peds.2017-2038D PMID 29437048 PMCID PMC5795516 Google Scholar Microsoft Academic

84. Siddique R, Liu Y, Nabi G, Sajjad W, Xue M, Khan S. Zika Virus Potentiates the Development of Neurological Defects and Microcephaly: Challenges and Control Strategies. Front Neurol [Internet]. 2019;10:319. Available from: https://www.frontiersin.org/article/10.3389/fneur.2019.00319 DOI: 10.3389/fneur.2019.00319 PMID 31024421 PMCID PMC6465516 Google Scholar Microsoft Academic

85. Dirlikov E, Major CG, Mayshack M, Medina N, Matos D, Ryff KR, et al. Guillain-Barré Syndrome During Ongoing Zika Virus Transmission - Puerto Rico, January 1-July 31, 2016. MMWR Morb Mortal Wkly Rep [Internet]. September 2016;65(34):910-4. Available from: https://www.cdc.gov/mmwr/volumes/65/wr/mm6534e1.htm DOI: 10.15585/mmwr.mm6534e1 PMID 27584942 Google Scholar Microsoft Academic

86. Olagnier D, Muscolini M, Coyne CB, Diamond MS, Hiscott J. Mechanisms of Zika Virus Infection and Neuropathogenesis. DNA Cell Biol [Internet]. June 27 2016;35(8):367-72. Available from: https://doi.org/10.1089/dna.2016.3404 DOI: 10.1089/dna.2016.3404 PMID 27348136 PMCID PMC4971419 Google Scholar Microsoft Academic

87. Fokke C, van den Berg B, Drenthen J, Walgaard C, van Doorn PA, Jacobs BC. Diagnosis of Guillain-Barré syndrome and validation of Brighton criteria. Brain [Internet]. January 1 2014;137(1):33-43. Available from: https://doi.org/10.1093/brain/awt285 DOI: 10.1093/brain/awt285 PMID 24163275 Google Scholar Microsoft Academic

88. Musso D. Zika Virus Transmission from French Polynesia to Brazil. Emerg Infect Dis [Internet]. 2015;21(10):1887. Available from: https://wwwnc.cdc.gov/eid/article/21/10/15-1125_article DOI: 10.3201/eid2110.151125 PMID 26403318 PMCID PMC4593458 Google Scholar Microsoft Academic

89. Richard AS, Shim B-S, Kwon Y-C, Zhang R, Otsuka Y, Schmitt K, et al. AXL-dependent infection of human fetal endothelial cells distinguishes Zika virus from other pathogenic flaviviruses. Proc Natl Acad Sci [Internet]. February 21 2017;114(8):2024-9. Available from: http://www.pnas.org/content/114/8/2024.abstract DOI: 10.1073/pnas.1620558114 PMID 28167751 PMCID PMC5338370 Google Scholar Microsoft Academic

90. Saiz J-C, Oya NJ, Blázquez A-B, Escribano-Romero E, Martín-Acebes MA. Host-Directed Antivirals: A Realistic Alternative to Fight Zika Virus. Viruses. 2018;10(9):453. Available from: https://www.mdpi.com/1999-4915/10/9/453 DOI: 10.3390/v10090453 PMID 30149598 PMCID PMC6163270 Google Scholar Microsoft Academic

91. Gómez LA, Montoya G, Rivera HM, Hernández JC. Características de la estructura molecular de las proteínas E del virus del Zika y E1 del virus de la rubéola y posibles implicaciones en el neurotropismo y en las alteraciones del sistema nervioso. Biomédica [Internet]. April 1 2017;37(Sup1):121-32. Available from: https://revistabiomedica.org/index.php/biomedica/article/view/3807 DOI: 10.7705/biomedica.v37i0.3807 PMID 28527274 Google Scholar Microsoft Academic

92. Honein MA, Dawson AL, Petersen EE, Jones AM, Lee EH, Yazdy MM, et al. Birth Defects Among Fetuses and Infants of US Women With Evidence of Possible Zika Virus Infection During Pregnancy. JAMA [Internet]. January 3 2017;317(1):59-68. Available from: https://doi.org/10.1001/jama.2016.19006 DOI: 10.1001/jama.2016.19006 PMID 27960197 Google Scholar Microsoft Academic

93. Fine Maron D. Zika Exposure Even after Birth May Lead to Brain Damage. Scientific American [Internet]. 2018 [Cited November 15 2019]. Available from: https://www.scientificamerican.com/article/zika-exposure-even-after-birth-may-lead-to-brain-damage/

94. Roberts DJ, Frosch MP. Zika and histopathology in first trimester infections. Lancet [Internet]. August 27 2016;388(10047):847-9. Available from: https://doi.org/10.1016/S0140-6736(16)30930-8 DOI: 10.1016/S0140-6736(16)30930-8 PMID 27372399 Google Scholar Microsoft Academic

95. Sousa AQ, Cavalcante DIM, Franco LM, Araújo FMC, Sousa ET, Valença-Junior JT, et al. Postmortem Findings for 7 Neonates with Congenital Zika Virus Infection. Emerg Infect Dis [Internet]. July 2017;23(7):1164-7. Available from: https://wwwnc.cdc.gov/eid/article/23/7/16-2019_article DOI: 10.3201/eid2307.162019 PMID 28459414 PMCID: PMC5512501 Google Scholar Microsoft Academic

96. Bonthius DJ. Lymphocytic Choriomeningitis Virus: An Underrecognized Cause of Neurologic Disease in the Fetus, Child, and Adult. Semin Pediatr Neurol [Internet]. 2012;19(3):89-95. Available from: https://www.sciencedirect.com/science/article/pii/S1071909112000034 DOI: 10.1016/j.spen.2012.02.002 PMID 22889536 PMCID PMC4256959 Google Scholar Microsoft Academic

97. Wallach E, Walther- Louvier U, Espil-Taris C, Rivier F, Baudou E, Cances C. Arthrogryposis in children: Etiological assessments and preparation of a protocol for etiological investigations. Arch Pédiatrie [Internet]. 2018;25(5):322-6. Available from: https://www.sciencedirect.com/science/article/pii/S0929693X18301106 DOI: 10.1016/j.arcped.2018.05.004 PMID 29914754 Google Scholar Microsoft Academic

98. Cao-Lormeau V-M, Blake A, Mons S, Lastère S, Roche C, Vanhomwegen J, et al. Guillain-Barré Syndrome outbreak

associated with Zika virus infection in French Polynesia: a case-control study. Lancet [Internet]. April 9 2016;387(10027):1531-9. Available from: https://doi.org/10.1016/S0140-6736(16)00562-6 DOI: 10.1016/S0140-6736(16)00562-6 PMID 26948433 PMCID PMC5444521 Google Scholar Microsoft Academic

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