



# Microcephaly and Zika virus: Neuroradiological aspects, clinical findings and a proposed framework for early evaluation of child development



Nelci Adriana Cicuto Ferreira Rocha<sup>a,\*</sup>, Ana Carolina de Campos<sup>a</sup>,  
Fellipe Cicuto Ferreira Rocha<sup>b</sup>, Fernanda Pereira dos Santos Silva<sup>a</sup>

<sup>a</sup> Department of Physical Therapy, Child Development Analysis Laboratory (LADI), Federal University of São Carlos (UFSCar), Rodovia Washington Luis, km 235, São Carlos, SP, 13565-905, Brazil

<sup>b</sup> Medical School, Pontifical Catholic University of Campinas (PUC-Campinas), Av. John Boyd Dunlop, s/n – Jardim Ipaussurama, Campinas, SP, 13060-904, Brazil

## ARTICLE INFO

### Keywords:

Microcephaly

Zika virus

Early development

Infant

International Classification of Functionality

Disability and Health

## ABSTRACT

**Background and aims:** As the recent outbreak of microcephaly cases caused by Zika virus has been declared a global health emergency, providing assessment guidelines for multidisciplinary teams providing early developmental screening and stimulation to infants with microcephaly is much needed. Thus, the aim of this manuscript is to provide an overview on what is known about neuroradiological aspects and clinical findings in infants with microcephaly caused by Zika virus and to propose a framework for early evaluation of child development.

**Methods:** The keywords “Zika virus” and “microcephaly” were searched in PubMed database for articles published from incept to May 2017. These texts were reviewed, and the ones addressing neuroradiological and clinical findings in infants were selected. Recommendations for early assessment were made based on the International Classification of Functionality Disability and Health (ICF) model.

**Outcomes and results:** The database search yielded 599 publications and 36 were selected. The studies detected microcephaly with diffuse brain malformations and calcifications, ventriculomegaly, optic nerve hypoplasia, macular atrophy, cataracts, impaired visual and hearing function, arthrogryposis, spasticity, hyperreflexia, irritability, tremors, and seizures, but very little is known about early development. Early assessments were described based on the ICF domains (Body Function and Structures, Activities and Participation and Contextual factors).

**Conclusion and implications:** Studies published showed abnormal brain, optic, neurologic and orthopedic findings, but very little is known about other aspects of functioning in infants with microcephaly caused by Zika virus. The biopsychosocial model based on the ICF paradigm provides an adequate framework to describe the condition of the infant with microcephaly receiving rehabilitative efforts to minimize disability. Efforts towards early identification of developmental delays should be taken within the first six months of life.

## 1. Introduction

Microcephaly is usually defined as a developmental defect of the brain, characterized by a significant reduction in the occipital-

\* Corresponding author at: Rua: José Riga, n.310 - Residencial Samambaia, São Carlos, SP, 13565-560, Brazil.

E-mail address: [acicuto@gmail.com](mailto:acicuto@gmail.com) (N.A. Cicuto Ferreira Rocha).

frontal head circumference (HC) at birth (Opitz & Holt, 1990) of at least 2 standard deviations (SD) below the mean for gestational age and gender (Ashwal, Michelson, Plawner, & Dobyns, 2009; Mochida, 2009; Thornton & Woods, 2009).

Microcephaly can be categorized as either congenital (primary) or of postnatal onset (secondary) (Ashwal et al., 2009; Gilmore & Walsh, 2013; Seltzer & Paciorkowski, 2014; Woods & Parker, 2013). Primary microcephaly may occur especially by 34 weeks of gestation (Woods & Parker, 2013), and may be caused by reduced neuronal proliferation or accelerated apoptosis, leading to simplification of the gyral pattern (Barkovich, Guerrini, Kuzniecky, Jackson, & Dobyns, 2012). Other forms of microcephaly are consistently associated with abnormal brain structure due to failure in neuronal migration in the 3rd–5th month of gestation (micro-lissencephaly, lissencephaly, schizencephaly, pachygyria, polymicrogyria) (Volpe, 2001). The causes are numerous, including genetic, syndromic, disruptive injuries, exposure to toxic substances during pregnancy, severe maternal malnutrition/deprivation (Baptista, Quaghebeur, & Alarcon, 2016; Woods & Parker, 2013), and intrauterine infections, such as toxoplasmosis, rubella, cytomegalovirus, herpes simplex and syphilis (Ashwal et al., 2009). Secondary microcephaly refers to acquired insults of the central nervous system (CNS) or to progressive metabolic/genetic disorders apparent in the first 1–2 years after birth (Ashwal et al., 2009; Gilmore & Walsh, 2013; Seltzer & Paciorkowski, 2014; Woods & Parker, 2013). It may be caused by disruptive injuries, infections, deprivation or genetic disorders affecting postnatal brain growth (Ashwal et al., 2009; Woods & Parker, 2013).

Currently, the Zika virus (ZikaV), a flavivirus transmitted by several species of *Aedes* mosquitoes, has been associated with an increased incidence of microcephaly in endemic areas in the Northeastern states of Brazil (Nunes et al., 2016).

The history of a ZikaV outbreak in Brazil in 2015 and the notifications of an unusual increase in microcephaly cases (Victoria et al., 2016) have motivated studies aiming to identify a possible causal relationship between microcephaly and ZikaV infection (Rasmussen, Jamieson, Honein, & Petersen, 2016). Evidence supporting this hypothesis includes the temporal and geographic association between the ZikaV outbreak and the cases of microcephaly (Oliveira Melo et al., 2016; Rasmussen et al., 2016). The Brazilian Ministry of Health (MOH) issued an epidemiology bulletin confirming 1.271 cases of microcephaly and others alterations in CNS from October 2015 to April 2016, suggesting congenital infection as the probable cause. Similar temporal association has also been identified in Colombia during epidemiologic weeks (January 31–November 12) in 2016 (Cuevas et al., 2016).

Several studies have supported a causal relationship between ZikaV infection and brain abnormalities. In humans, ZikaV RNA was detected in amniotic fluid (Calvet et al., 2016), fetal brain tissue and placenta (Bhatnagar et al., 2017), and in blood and other tissues (PAHO & WHO, 2015), indicating that Brazilian ZikaV crosses the placental barrier causing microcephaly. Recent experimental studies by Garcez et al. (2016) and Souza et al. (2016) demonstrated that ZikaV induces cell death in human neural stem cells, disrupts the formation of neurospheres, reduces the growth of organoids and reduces cell proliferation. Furthermore, ZikaV seems to infect preferentially more precursor cells than neurons (Retallack et al., 2016), indicating that infection in the first trimester of brain development may result in severe damage. Evidence from an animal model showed ZikaV genomic RNA in several tissues of newborn mice, especially in the brain, with findings of cortical malformations, reduced cell number and cortical layer thickness, whole-body growth delay, intra-uterine growth restriction, lower skull length, cranial height and biparietal diameter (Cugola et al., 2016).

Altogether, these studies support a strong causal relation between ZikaV infection and brain abnormalities and reinforce the idea that ZikaV not only causes microcephaly, but a congenital syndrome. Although there is confirmation of affinity of ZikaV to brain tissue (Tang et al., 2016), other studies are necessary to further characterize the consequences of ZikaV infection during different stages of fetal development and post natal.

This critical review has been motivated by the alarming scenario of microcephaly caused by ZikaV in Brazil, and the urgent need to identify the main clinical findings in infants so developmental delays can be detected early. Thus, the aims of this study are to provide an overview on what is known about neonatal neuroradiological aspects and clinical findings in infants with microcephaly caused by ZikaV, and to propose a framework for early evaluation of child development.

The Center for Diseases Control (CDC) has recently published recommendations for the evaluation and management of infants with possible congenital ZikaV infections (Russell et al., 2016). However, the guidance emphasizes the biomedical model of disease, with a focus on laboratory testing and clinical evaluation. It is known that field of pediatric rehabilitation has undergone major conceptual changes in the past few decades with the introduction of a new framework to explain human functioning, provided by the ICF (Camargo, 2016). The ICF uses a biopsychosocial approach to describe functioning and disability as the dynamic interactions between body functions/structures, activities and participation domains. Contextual factors such as environmental and personal factors also have major influence on disability and health (WHO, 2001). The main implication of this new framework is that the traditional biomedical model, which focuses on disability, abnormality and limitation, no longer meets the health professionals' needs towards understanding the complexity of individual's lives. In this context, current assessment and rehabilitation approaches should take biopsychosocial factors into account in order to promote optimal capacity and full participation of the individual in all aspects of life (dos Santos, Pavão, de Campos, & Rocha, 2012; Palisano et al., 2012; Rosenbaum & Gorter, 2012).

The surveillance status recommended by the WHO due to the unknown features of ZikaV infection requires the implementation of precautionary and preparatory measures. Among these measures, a central point is to design a framework to be used by multi-disciplinary teams when providing developmental screening and stimulation to infants with microcephaly. Therefore, in this review, the International Classification of Functioning, Disability and Health (ICF) model will be used as guidance for clinicians and researchers to identify relevant outcomes during assessment that will support early intervention planning and family-centered actions.

## 2. Methods

This was a non-systematic review article conducted by a panel of experts. The keywords “Zika virus” and “microcephaly” were searched in PubMed database for articles published from inception to May 2017. Manuscripts were excluded if they addressed the

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