DOI: 10.1590/1413-812320152110.16832016

Microcephaly and other Zika virus related events: the impact on children, families and health teams

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Abstract *The present study aimed to present an overview of recent national and international research on the Zika virus (ZIKV), as well as to explore possible action plans focused on children, their families and the health teams involved. Therefore, the study proposes the implementation of tracking systems in order to identify, describe and characterize the potential correlates of prenatal exposure to ZIKV, divided into three lines of action: 1. Diagnostic and etiological evaluation as well as screening of developmental problems in children confirmed or suspected of prenatal ZIKV infection. 2. Investigation of the emotional impact, quality of life, coping strategies and support network of the affected children and their families. 3. Training of multidisciplinary teams to conduct assessments and intervention programs throughout these children's development, especially in the first three years of life. In conclusion, the recent ZIKV outbreak in Brazil and several other Latin American countries places a significant burden on the health care systems: to understand the real meaning of a potential new teratogen; to unravel the pathogenic mechanisms of ZIKV, particularly in a prevention perspective; and to recognize the broad spectrum of clinical manifestations in order to devise intervention programs.*

Key words *Public Health, Microcephaly, Health care*

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Introduction

Studies on the Zika virus (ZIKV) have focused on the biological processes of infection and transmission, considering the effect on the neurological development of the child with ZIKV-related microcephaly related. Indeed, a thorough and lengthy document produced by the Brazilian Health Ministry(MS) entitled *A Protocol for the Surveillance and Response to the Occurrence of Microcephaly Related to Zika Virus Infection*[1] presents the epidemiology of the infection of the virus in humans, defines microcephaly, diagnostic methods and the neonatal manifestations. In addition, a number of recent publications of clinical investigations carried out by Brazilian authors in scientific journals in Brazil and abroad have described the identification of prenatal microcephaly[2],eye abnormalities[3] and other congenital malformations[4].

This and other information has also raised the suggestion that the criteria used by the MS to identify the presence of microcephaly in newborns is sensitive enough but not very specific, so most children suspected of having the virus will not have the diagnosis confirmed[5]. Of the recent series of 5909 suspected cases (recorded between November 2015 and February 2016), 1687 underwent complete clinical investigation, with 641 cases of microcephaly and/or an alteration of the central nervous system suggestive of a congenital infection being confirmed. Of the confirmed cases, laboratory analysis identified ZIKV in 82 living children and 31 fetal losses. This clinical observation is supported by the fact that the ZIKV can lodge in the cerebral cortex and brainstem of fetuses diagnosed with microcephaly, among other abnormalities[6,7] such as intracranial calcifications, dilation of the cerebral ventricles or a modified posterior fossa. Of the remaining cases, 1046 were found not to be ZIKV related, but the enormous number of 4222 cases remain under investigation[8]. As these are the least affected, the heavy burden of a thorough assessment protocol, directed at the children and families and for the health system, may not be justified[8].

On the other hand, some researchers argue that the increase in cases of suspected microcephaly stems from several factors: a) catching up with the previously unreported cases: it is estimated that 2/3 of the cases of congenital anomalies are usually not reported and a more active search has uncovered a number of previously unreported cases; b) the adoption of the systematic observation of head circumference (HC) compared with gestational age, which was not previously done routinely in all neonatal units; c) head circumference reference curves are not those of the study population; d) the assumption of a normal distribution of HC by gestational age, which might not be true; e) a definition of microcephaly by measuring the HCat -2 SD or 3rd percentile: most children with a HD between -2 SD/-3SD showed no evidence of malformations[5,9].

Another crucial issue raised by researchers with experience in epidemiological research of congenital malformations, both in Brazil and in other Latin American countries, was that support for the evidence that embryopathy caused by the ZIKV is responsible for the cases of microcephaly is weak. For this reason, the prestigious Latin -American Collaborative Study of Congenital Malformations published on its website a series of technical notes which detail the difficulties in definitively establishing this association. This study group proposed the method of case-cohort study with flow chart, including the investigation of STORCH infections and other potential teratogens such as fetal alcohol syndrome and the dozens of genetic syndromes, from chromosomal abnormalities identified by karyotyping, such as microdeletions and microduplications identified by genomic array techniques to monogenic disorders identified by the techniques known as *next generation sequencing*[9,10].

The aforementioned scientific literature has been widely reflected in the Brazilian media, but neither the former nor the latter have devoted the same level of attention to the follow-up of these children, the social impact of their diagnosis, the emotional and financial burden on families nor the preparation (or lack thereof) of health teams to face the challenge of assessing and instituting intervention methods over time. As stated in an editorial in the Lancet of February 3 with the provocative title, *Brazil-the unexpected opportunity that Zika presents*[11] an epidemic has the power to make profound changes in the public health policies of a country. It is up to all of us try to further them.

Our view is that we should establish monitoring systems to understand, describe and characterize the issues that are correlates of prenatal exposure to ZIKV. We see three main areas for action: 1 - Diagnostic and etiological evaluation as well as screening of developmental problems in children reported as confirmed or suspected cases; 2 - investigation of the emotional impact, quality of life, coping strategies and support

networks of families of affected children; 3 - training of multidisciplinary teams to evaluate and develop intervention programs throughout the development of these children, especially in the first 3 years of life.

In respect of these areas of action, two reports from *the Centers for Disease Control and Prevention* (CDC/USA)[12,13] were published in 2016, with recommendations for the screening of pregnant women, newborns and children with possible congenital ZIKV infection. The main measures are: notification of any case to the responsible authorities; a hearing assessment at 6 months, with monitoring of any changes found and evaluation of head circumference and developmental milestones during the first year of life. A specialized multidisciplinary team including neuropediatricians and motor area and language therapists, among others, should carry out follow -up. It is worth noting that the report proposes the specific monitoring of children only when the mother and child have positive results from viral testing. When the mother has a positive result and the child a negative result for ZIKV, the CDC recommends only routine monitoring of the child. However, the lack of knowledge and information about the effects of maternal infection on the fetus in the medium and long term suggests the close and systematic monitoring of all children of infected mothers. This initiative can contribute greatly to a better understanding of the action of the virus and its consequences. At the moment, the specific serological tests for the diagnosis of ZIKV are not available in Brazil's Unified Health System (SUS). This makes it even more essential to develop a monitoring system of infants reported with decreased head circumference, at least for those below the third standard deviation, even without evidence of actual neurological damage. This measure could contribute to the identification of forms without further anatomical changes, but with impairments in other developmental areas in the long term. The model for fetal alcohol effects clearly shows this type of result[14] In other words, it is expected that children exposed in utero to ZKV may manifest a range of problems, from complex syndromes with multiple disabilities to learning difficulties in school and problems of social adaptation, without necessarily an altered morphological phenotype.

The effects most commonly associated with microcephaly are related to intellectual impairment and other conditions including epilepsy; cerebral palsy; delayed development of language and /or motor skills; strabismus; and eye, heart, renal and urinary tract disorders, among others. The establishment of a differential diagnosis of genetic causes and other environmental teratogens such as prenatal infections, prenatal exposure to alcohol, X - rays and some medicines should be made, since microcephaly can be observed in all of these conditions[15]. Ophthalmological findings have also been reported. A Brazilian study described the case of three mothers who had no eye injury, but their three children had unilateral lesions of the macular region[3]. Subsequently, the same group described the same finding in a group of 10 children with microcephaly associated with ZIKV[16], which highlights the need to monitor visual problems in this group.

Specific indicators have not yet been established for the cognitive and behavioral impairment of children infected with ZIKV. However, from clinical case reports in the literature, it appears that this group will require early intervention considering the multiple risks caused by global neurodevelopmental changes, along with its high impact on the adaptive functioning of these children. The Brazilian Inclusion of People with Disabilities Act n.13.146 (Status of Persons with Disabilities) was established on July 6, 2015 to ensure and promote, on equal terms, the rights and fundamental freedoms of disabled people, aimed at their social inclusion and citizenship. It is up to the State, society and the family to guarantee to the person with disabilities the realization of their rights to life, health, education, social security and rehabilitation, among others, and to ensure their personal, social and economic well-being[17].

For these reasons, monitoring studies are fundamental to identify the diverse types of damage to children suspected of having been exposed to agents that are potentially harmful to the developing nervous system. Therefore, it is important that structured assessment protocols are used, particularly those validated and standardized for the Brazilian population. In the first 6 months of life, the fundamental characteristics that must be observed are aspects of physical development (such as weight, height, and head circumference growth), motor skills (the presence and disappearance of primitive reflexes at the expected time and the ability to support the head, pick up objects, put objects into the mouth, and develop trunk control), expressive and receptive language skills (babbling, looking toward sounds, recognizing one's name) and cognitive and social skills (emitting social smiles, recognizing familiar pe-

ople, following moving objects, reacting to the interactions and expressions of caregivers).

By the end of the next 6 months of life, other characteristics frequently present are: turning around and sitting up, crawling or standing with support (motor area); production of language syllables, understanding yes and no, using vocalization to intentionally draw the attention of adults and responding to simple verbal commands (language area); early recognition of objects, starting to search for hidden objects, development of joint attention when looking at targets indicated by the caregiver, use of objects with social function (cognitive and social area).

By the time a child reaches two years of age, the following features are now often present in typical development: being able to walk without support, stacking blocks; in the area of language, pronouncing words and putting them together in short sentences, recognizing the names of others; in the cognitive and social area, interacting with other children during play, starting to play with objects properly (like dolls or toy cars), getting to know colors. By the age of three, it is expected that the child can run, hold chalk or a pencil (motor skills); pronounce phrases with 3 or 4 words, know how to say their name (language skills); can play games with simple rules, start to understand taking turns in games, have spontaneous positive interactions with friends or family (social and cognitive skills)[18].

The recognition of these and other changes during the development of children requires intervention actions. These should be prospective in nature and should also involve an assessment of patterns of behavioral functioning and indicators of social and family adaptation. The monitoring of the family to check mental health indicators, as well as social support and quality of life are fundamental in the care of children with developmental disorders, especially when associated with an intellectual deficit. Indeed, daily living with a child with a chronic condition can change family functioning, directly affecting the quality of life. On the other hand, social support is an important protective factor and promoter of mental health in the parents of these children. Socioemotional support assists in developing coping strategies for handling the difficulties of daily life of parents of children with an intellectual deficit. Thus, in addition to monitoring the child, due regard must be given to the support of groups of parents, and to checking for indicators of emotional and quality of life problems, and building a social support network to promote the mental health of the family[19-22].

There needs to be an effort by the scientific community and health services to evaluate and monitor this particular group using instruments validated for Brazil and to incorporate such assessments into the care of children and families. Capacity building and training should be offered and facilitated for professionals, from the definition of priorities and the establishment of a follow-up program. Thus, following the same line as the CDC/USA[12,13] a care protocol in the short, medium and long term can guide the action of all those involved in the evaluation of and specialized intervention for children and families affected by ZIKV. Particular care should be targeted toward mothers and other relatives responsible for taking the children to specialized services. The medical, educational and psychological support which these families need should be put in place considering the possible developmental losses that can arise in children affected by ZIKV.

In conclusion, we can say that the Brazilian population, as well as the health care system in general, is facing a major challenge which is to understand the real meaning of a potential new teratogen. Unravelling the pathogenic mechanisms of ZIKV is essential for the development of preventative strategies. Recognizing the broad spectrum of clinical manifestations, mainly the impact on the cognitive-behavioral development is critical to develop intervention programs aimed at providing the best care to the children and families affected.

Collaborations

D Brunoni, SM Blascovi-Assis, AAC Osório, AG Seabra, CAH Amato, MCTV Teixeira, MM Rocha and LRR Carreiro participated in the design and conception of the research and the review of the final text.

Acknowledgments

Other members of the faculty of the Graduate Program in Development Disorders at Mackenzie Presbyterian University are co-authors of the text, namely: Cristiane Silvestre de Paula, Elizeu Coutinho de Macedo, José Salomão Schwartzman, Miriam Oliveira Ribeiro, Maria Eloisa Famá D´Antino, Paulo Sérgio Boggio, Roberta Monterazzo Cysneiros, Sueli Galego de Carvalho

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Article submitted 10/03/2016
Approved 25/06/2016
Final version submitted 27/06/2016