

Autistic spectrum disorder in children exposed to the zika virus in pregnancy: a possibility?

Transtorno do espectro autista em crianças expostas ao vírus zika na gestação: uma possibilidade?

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ABSTRACT

This study aimed to describe the neurodevelopmental of children born to mothers exposed to Zika virus (ZIKV) without birth defects. Nine children aged 20 to 46 months were assessed by the Bayley III Scales. Of these, one child had tested positive ZIKV-IgG, whilst the others had negative results. All children underwent neuropsychiatric evaluation and some had magnetic resonance imaging. Six children had developmental changes (language delay was observed in all of them); four with Autism Spectrum Disorder and two motor and language delay. Three children obtained satisfactory results in Bayley-III. The results shed light on the hypothesis that cognitive changes observed in five children maybe related to exposure to the effects of ZIKV infection on the maternal environment.

Keywords: zika virus infection, child development, bayley iii scales, congenital zika syndrome, cognition.

RESUMO

Este estudo teve como objetivo descrever o neurodesenvolvimento de crianças nascidas de mães expostas ao vírus Zika (ZIKV) sem defeitos congênitos. Nove crianças de 20 a 46 meses foram avaliadas pelas Escalas Bayley III. Destas, uma criança teve resultado positivo para ZIKV-IgG, enquanto as demais tiveram resultado negativo. Todas as crianças foram submetidas à avaliação neuropsiquiátrica e algumas fizeram ressonância magnética. Seis crianças apresentaram alterações no desenvolvimento (o atraso de linguagem foi observado em todas); quatro com Transtorno do Espectro Autista e dois com atraso motor e de linguagem. Três crianças obtiveram resultados satisfatórios no Bayley-III. Os resultados lançam luz sobre a hipótese de que as alterações cognitivas observadas em cinco crianças podem estar relacionadas à exposição aos efeitos da infecção pelo ZIKV no ambiente materno.

Palavras-chave: infecção pelo vírus zika, desenvolvimento infantil, escalas bayley iii, síndrome congênita do zika, cognição.

1 INTRODUCTION

An outbreak of Zika virus (ZIKV) infection was first reported in northeast Brazil in early 2015 (CAMPOS *et al.*, 2015). The rapid spread of the epidemic led the World Health Organization (WHO) to declare ZIKV to be a public health emergency of international concern (MUSSO *et al.*, 2016).

The association of congenital ZIKV infection with cases of microcephaly (DE CARVALHO *et al.*, 2016) has drawn worldwide attention to the mechanisms of this viral illness, its pathogenesis and exposure prevention. Subsequently, several studies confirmed other birth defects associated with congenital ZIKV infection (RASMUSSEN *et al.*, 2016).

All of these findings heightened awareness of the serious risk of ZIKV infection, making it one of the most serious congenital infections. Since 2016, surveillance remains

active to identify and monitor pregnant women with possible Zika virus exposure. Despite the significant increase in publications on ZIKV in recent years, there are still few longitudinal studies focusing on neurodevelopment of children whose mothers were exposed to ZIKV during pregnancy. Investigations regarding the development of this group of neonates, including those with no obvious malformations, are needed.

The evaluation and monitoring of neuropsychomotor development of at-risk newborns due to congenital ZIKV infection or exposure allows preventive action and referral to specific treatments since early detection of changes (SILVA *et al.*, 2011).

This study aimed to describe the neurodevelopment of children born to mothers exposed to ZIKV, without microcephaly or other birth defects.

2 MATERIALS AND METHODS

2.1 STUDY DESIGN

We carried out a descriptive case series study with a non-probabilistic convenience sample.

This research was conducted at Professor Nelson Barros Maternal Child Outpatient Clinic, Federal University of Bahia in Salvador, Bahia, Brazil during the period from October 2017 to August 2019.

2.2 EXCLUSION CRITERIA

The INTERGROWTH-21st standards for gestational age and sex were considered for head circumference measurement, within 2 standard deviations (SD) to be regarded normocephalic at birth (VILLAR *et al.*, 2014). Weight under 2,500g; obstetric complications, perinatal anoxia, prematurity, congenital neurological changes; head trauma; genetic syndromes; chronic heart, lung, digestive or metabolic diseases; maternal use of prescription drugs; alcohol, tobacco or other psychoactive substances; positive or inconclusive results for other congenital infections and malformations in any organ system; family history of autism or schizophrenia were excluded.

2.3 PARTICIPANTS

We identified 20 potential infants to participate in the study. Some subjects were excluded: (i) one due to extreme prematurity; (ii) another child had a diagnosis of cerebral palsy with a family history of severe intellectual disability (sibling); (iii) two infants had congenital infections: one with toxoplasmosis and the other with cytomegalovirus; and,

(iv) one child with congenital hypothyroidism (who had begun treatment at eight months age). Five children were excluded from this study because their parents had negative results for ZIKV infection. One child dropped out of study. Nine children completed the assessment protocol.

Of the eight children evaluated, six were male and aged between 20 months and 13 days and 46 months and 10 days, with an average of 30,6 months. All mothers presented negative serology for TORCHS and immunoglobulin G (IgG) positive for postpartum ZIKV. One of them (case 8), asymptomatic, underwent serology during pregnancy with positive IgM and IgG ZIKV. The other mothers had symptoms corresponding to infection during pregnancy, with skin rash being the most frequent. Clinical and socioeconomic data are described in Tables 1 and 2, respectively.

Table 1. Clinical characterization of the sample and Bayley III Scales composite scores

Case	Maternal ZIKV IgG	Infection week	Infection Quarter	Sex	GA	HC	APGAR 1'	APGAR 5'	BW	Cognition	Language	Motor	Neuropediatrician diagnoses
1	Positive	3	1	F	40	36	9	10	3460	95	71*	91	NDD
2	Positive	30	3	F	39	38	5	9	3705	130	118	127	TD
3	Positive	16	2	M	41	35	9	10	3022	100	91	97	TD
4	Inconclusive	20	2	M	40	35	8	9	3550	85	65*	67*	NDD
5	Positive	20	2	M	39,5	35	9	9	3816	95	124	97	TD
6	Positive	30	3	M	40	33,5	5	8	3338	70*	53*	76*	ID/ASD
7	Positive	30	3	M	42	38	8	9	3600	55*	47*	46*	ID/ASD/Epilepsy
8	Positive	38	3	M	40,1	36	10	10	3350	95	71*	94	ASD
9	Positive	18	2	M	42	34	8	9	3400	85	65*	70*	ASD/ID

GA - Gestational age; BW - Birth weight; HC - Head circumference; NDD - Neuropsychomotor developmental delay; TD - Typical development; ID - Intellectual Disability; ASD - Autism Spectrum Disorder; * Developmental delay.

Source: Own Authorship

Table 2. Sociodemographic data

Case	Maternal Schooling	Maternal age at conception	Paternal age at conception	Socioeconomic status
1	University	28	31	B1
2	University	35	35	B2
3	Hight School	35	38	C2
4	Elementary	16	19	D-E
5	University	32	38	B1
6	Hight School	34	39	C1
7	Hight School	29	24	C2
8	Hight School	32	44	C2
9	Elementary	26	36	C2

Source: Own Authorship. Socioeconomic status based on Brazil Criterion – ABEP, 2015

Eight children had negative ZIKV IgG, while one (case 7) tested positive. All children had negative IgG for dengue virus (DENV) by serological tests. Enzyme-linked immunosorbent assay kit (Euroimmun, Lubeck, Germany) and fluorescence

immunoassay for qualitative measurement of ZIKV and DENV specific IgG and IgM antibodies (Eco Diagnóstica, Minas Gerais, Brazil) were used.

2.4 INSTRUMENTS AND PROCEDURES

The parents / guardians were informed about the research. In case of agreement to participate in the study, they signed the Free and Informed Term of Consent approved by the Ethics Committee on Research with Human Beings of the Institute of Health Sciences / UFBA.

All children were evaluated in the presence of their guardian (s) at a scheduled time. The parents / guardians were asked to answer the Socioeconomic Assessment Questionnaire (ABEP, 2015) and also to provide information on gestational data, birth, development, general health and family structure; Lipp's Adult Stress Symptom Inventory (ISSL) was performed (LIPP, 2000) assessing physical and psychological symptoms of adult stress.

Confirmation of data regarding pre- and perinatal periods and child development was performed through prenatal laboratory and obstetric ultrasound, the pregnant woman's card, report of hospital discharge after childbirth, child's card / child health handbook and birth record.

The interview and assessment of child development lasted from 2 to 2 ½ hours, according to the child's willingness, interest and engagement.

Cognitive development, language and motor skills were assessed with the Bayley Scales of Infant and Toddler Development, third edition (BSID-III), third edition. This instrument was translated and cross-culturally adapted to Brazil (MADASCHI *et al.*, 2016). The BSID-III assessment was applied by a neuropsychologist.

BSID-III scales are recognized among the best tools for evaluation in research and clinical contexts, providing the identification of possible developmental delays due to their solid theoretical basis and well-delineated psychometric properties (WEISS *et al.*, 2017). BSID-III evaluate cognition, language (expressive and receptive communication), motricity (refined and broad), social-emotional development, and the adaptive component. In this study, the cognitive, motor and language scales were used, considering the composite score. BSID-III ranks development into standard scores ranging from 40 to 160 points across all its subscales. The normative mean average is considered 100, with a standard deviation of 15 points (BAYLEY, 2006).

BSID-III categorizes composite scores as much higher if at or above 130 points; higher, score between 120 to 129 points; medium high between 110 to 119 points; medium high between 90 to 109 points; medium low between 80 and 89 points; between 70 and 79 points and at or below 69 extremely low. Results equal to or less than two standard deviations from the mean (i.e. <70) are considered as developmental slowing (BAYLEY, 2006). It is also considered the age of development, represented by the average of the expected raw score for that age.

All children were evaluated by a neuropsychiatrist. The result of the cranial magnetic resonance image (MRI), when performed, was described.

Parents were informed about the results of the evaluation and were given a printed report and guidelines for child development stimulation. In those cases, in which changes were found, the pediatrician was reported, and the child referred for assessments and for early stimulation rehabilitation.

The data were organized in tables using absolute frequency, standardized scores and categories defined by the tests and instruments used. The results were explored and analyzed qualitatively.

3 RESULTS

All mothers had prenatal follow-up, with no reports of complications, identified by anamnesis and pre and perinatal exams.

One child (case 4) presented altered hearing screening tests after birth and later right ear hearing mild loss was confirmed through the transient evoked otoacoustic emissions (TEOAE).

In all cases, maternal infection occurred during the outbreak period and was presumed from clinical history including gestational skin rash (except for case 8, whose mother's infection was asymptomatic) and confirmation by subsequent laboratory examination (IgG).

Among the nine children, five presented slowing in at least one area of development, whilst language delay was present in all. Three children had altered neuropsychological testing in all areas evaluated. The child with confirmed congenital infection presented late microcephaly and decreased development. Three children had typical development. Table 2.

Cases 1, 4 and 6 presented worse performance in receptive communication, with a difference of 10, 12 and 37 months, respectively, between chronological (20, 22 and 44

months) and developmental (10, 10 and 7 months) ages. Cases 7, 8 and 9 achieved the worst scores in expressive communication, with distances of 42, 13 and 23 months from chronological ages (46, 28 and 40 months), respectively, and performance compatible with ages 2, 15 and 17 months, respectively. Cases 1 and 4 had better performance on cognition and cases 6, 7 and 8 in the gross motor domain. The case 9 performed better on fine motor domain. Table 3 details the raw scores of the BSID - III subtests and the corresponding developmental ages of all cases.

Table 3. Performance characterization by cognitive function and equivalent developmental age on the Bayley III Scales

Case	Age at assessment	HC at assessment	Cognition	Receptive Communication	Expressive Communication	Fine Motor	Gross Motor	Developmental delay
1	20	47,5	53/ 18 +	13/10 *	18/15 *	33/17 +	51/18 +	Yes
2	30	53	80/ 42 +	36/35 +	42/40 +	51/40 +	63/35 +	No
3	23	47,5	61/ 23 +	20/18 +	28/22 +	37/22 +	55/21 +	No
4	22	48	53/ 18 +	13/10 *	18/15 *	33/17 *	42/12 *	Yes
5	23	48	60/22 +	29/26 +	38/34 +	37/22 +	55/21 +	No
6	44	50	56/20 *	11/7 *	20/17 *	27/10 *	67/42 +	Yes
7	46	47	17/4 *	10/6 *	5/2 *	22/ 7 *	36/9 *	Yes
8	28	50,5	68/ 27 +	21/19 *	18/15 *	40/26 +	60/42 +	Yes
9	40	49,5	70/29 +	25/22*	21/17*	46/33 +	50/17*	Yes

Age at assessment in months; HC - Head circumference at assessment; Gross scores / corresponding age in months; (*) Delay; (+) Score within the middle zone for age considering 2 standard deviations
Source: Own Authorship

Clinical neurological evaluation indicated decelerated neuropsychomotor development in two children and Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) (APA 2013) diagnosis of Autistic Spectrum Disorder (ASD), with intellectual impairment in three cases (6, 7 and 9); one of them with late microcephaly and epilepsy, characterized by perceptive seizures. Another child (case 8) was diagnosed with ASD without intellectual impairment. The others presented typical neurodevelopment, as can be seen in Table 4.

Table 4. Cranial magnetic resonance imaging findings according to neurological diagnosis

Case	Infection quarter	MRI	Postnatal microcephaly	Neuropediatrician Diagnoses
1	1	Small sequelae areas of encephalomalacia surrounded by gliosis and with adjacent perivascular spaces in the left peri-atrial region and in the left frontal radiated crown.	No	NDD
4	2	Not performed	No	NDD
6	3	Normal	No	ID/ASD
7	3	Signs of supratentorial hydrocephalus and small diffuse brain volumetric reduction in the cortico-subcortical area of encephalomalacia / gliosis in the right occipital parietal region, relative	Yes	ID/ASD/Epilepsy

		hypomyelination / delay of white supratentorial myelination.		
8	3	Normal	No	ASD
9	2	Not performed	No	ID/ASD

NDD - Neuropsychomotor developmental delay; Intellectual Disability – ID; Autism Spectrum Disorder – ASD

Source: Own Authorship

Table 4 shows changes in cranial magnetic resonance imaging (MRI) in cases 1 and 7.

4 DISCUSSION

In this study, we presented nine cases with physical exams and pre- and perinatal evolution without abnormalities, with presumed exposure to intrauterine ZIKV. Prenatal ultrasound showed no changes, and all were born with adequate weight and head circumference, no birth defects or any sign of congenital ZIKV syndrome (CZS).

The presumed vertical transmission occurred in one of the children (case 7), whose performance in BSID-III was the most compromised of the sample. Infection occurred in the third trimester, during which time some studies suggest less neurodevelopmental impairment and milder cognitive impairment (WHEELER, 2018). However, central nervous system (CNS) abnormalities in late congenital ZIKV infections reinforce CNS viral tropism (BRASIL *et al.*, 2016) and draw attention to the high risk of infection at any stage of pregnancy. In case 7, MRI alterations and global developmental retardment were also identified, and the diagnosis of ASD with intellectual impairment was confirmed by the neuropediatric evaluation. These findings are compatible with the study by Brasil *et al* (2016), showing brain changes in 10 children whose infection occurred between 30 and 39 weeks of gestation. Cerebral calcifications, cerebral atrophy, ventricular enlargement and hypoplasia of brain structures were described by these authors in infected children up to the 34th week of gestation. Parenchymal brain hemorrhages have been reported in a child whose mother was infected at the 39th week of gestation (BRASIL *et al.*, 2016). For this case, neuronal toxicity is considered as a hypothesis. Adams Waldorf *et al* (2018) reported that, in monkeys, the teratogenic action of ZIKV infection is severe and leads to long-term effects including loss of brain volume, fetal progenitor cells, ependymal epithelial damage, and changes in brain functions and behavior, also corroborated by Mavigner *et al* (2018).

In the other cases, congenital infection was not confirmed by laboratory tests in children, suggesting that exposure to maternal immune response to the virus during pregnancy was the possible risk factor for child development (VALENTINE *et al.*, 2016; FELIX *et al.*, 2017). In case 1, maternal infection occurred early in pregnancy and, although child's diagnosis was not confirmed for ZCS, MRI revealed changes, and reduction in expressive and receptive communication was observed. In a study of 117 children (BRASIL *et al.*, 2016), infections that occurred during the first trimester suggested similar MRI findings. Another hypothesis concerns the fact that changes in the fetal environment resulting from maternal infection may interfere with fetal neuronal response (CHATTERJEE *et al.*, 2001; MAWSON, 2016).

Even in the absence of fetal infection, it is known that infections during pregnancy affect the fetal environment due to maternal fever, dehydration, reduced fetal blood supply, nutritional change and other symptoms. Placental damage may occur from infection. Almost half of preterm births are associated with histological evidence of placental inflammation (CHATTERJEE *et al.*, 2001). In addition, during pregnancy, the presence of complications may reduce fetal blood supply, leading to the shedding of blood from peripheral regions to the central nervous system (CNS) (CHATTERJEE *et al.*, 2001; VIANNA *et al.*, 2018). Other studies corroborate the association between exposure to maternal infections and changes in fetal brain and behavioral development due to infections and intrauterine inflammatory processes (DOHERTY, 2007; PATTERSON, 2011; VIANNA *et al.*, 2018). These studies suggest that proinflammatory cytokines would damage oligodendrocytes at critical periods of fetal brain development, causing brain damage. Thus, there appears to be a direct relationship between the nervous and immune systems, such as a neuroimmune network that influences many mental disorders (VIANNA *et al.*, 2018). Study points that CNS can regulate the immune system through neuronal and hormonal pathways, and also be influenced through cytokine production. The immune system can modulate brain function and influence neurogenesis in response to infectious and inflammatory processes (VIANNA *et al.*, 2018). According to experimental studies, CNS inflammation, caused by the production of cytokines by the mother or fetus, may lead to modification of brain activity in regions such as the hippocampus (MONJE *et al.*, 2003; DOHERTY, 2007; PATTERSON, 2011; VIANNA *et al.*, 2018).

Case 4 presented slowed motor and language development and was diagnosed with neuropsychomotor developmental lagging. The mother of this child had clinical

manifestations suggestive of Zika infection, with significant skin rash in the twentieth week of pregnancy, despite an inconclusive IgG result. Hearing loss was identified in the right ear of the child. The association between ZIKV and hearing loss has been described (LEAL *et al.*, 2016), but to date, to the best of our knowledge, there are no studies confirming hearing loss in exposed children without ZIKV serological confirmation.

Retard in language and motor skills and poor performance in BSID-III was seen in case 6. The neuropsychiatric evaluation confirmed ASD, with associated intellectual impairment. Case 8 presented with slow down language development and met DSM-5 (APA, 2013) criteria for ASD, with preserved cognition and motor skills. Vianna *et al.* (2018) suggested an association between the immune system and ASD, as well as other investigators (FORTIER *et al.*, 2007; KALKBRENNER *et al.*, 2010; ASHWOOD *et al.*, 2011; BUSINARO *et al.*, 2016) linking ASD, maternal infections and inflammatory profile. The relationship between proinflammatory cytokines and neuropsychiatric diseases has been studied (MARQUES *et al.*, 2007).

Language delay was identified in six children with developmental lateness. Of these, three presented clinical signs suggestive of ASD. Russo *et al.* (2018), by means of induced pluripotent stem cells derived from three individuals with nonsyndromic ASD, investigated neuronal connectivity and interaction between neurons and astrocytes. They observed that TEA-derived astrocytes interfered with adequate neuronal development and associated interleukin-6 secretion by astrocytes from individuals with ASD as possibly responsible for neural defects in these individuals (RUSSO *et al.*, 2018). To date it is not clear how the immune system response to ZIKV infection is regulated; therefore, further studies in this regard are suggested.

Recent non-human primate studies have demonstrated the important teratogenic action of ZIKV infection in the fetal brain, with lasting effects such as reduced brain volume and loss of neuronal progenitor cells, and changes in brain behavior and functions. It is assumed that there is a spectrum ranging from exposure to maternal infection with mild cognitive impairment to more severe CZS (ADAMS WALDORF *et al.*, 2018; MAVINGER *et al.*, 2018) Behavior and emotional regulation should be monitored in future research to describe the risk of developing psychopathology.

A recent study (CARVALHO *et al.*, 2020) reported 27 cases with clinical and neuroradiological features of SCZ in children with negative ZIKV serology, whose mothers had symptoms of ZIKV infection during the epidemic in Brazil. In this study, five children whose mothers had ZIKV infection during pregnancy showed developmental

delay in the absence of biological confirmation of ZIKV infection. These findings suggest permanent ZIKV-related neurodevelopmental damage, still poorly understood. The possibility of immune response uncontrolled, caused by ZIKV bringing damage to the system central nervous is under study (LIMA *et al.*, 2019).

Three children had adequate development. However, it cannot be said that they will remain so at other stages of development or stay with completely intact brain structures, since they did not perform MRI. Two-case study reported MRI changes in children exposed to ZIKV during pregnancy without congenital infection and with no developmental delay as shown by clinical evaluation (FELIX *et al.*, 2017)

Similar results were observed in children exposed to ZIKV without microcephaly. Ten out of 56 exposed children without microcephaly had developmental slowing, as assessed by BSID-III, especially on motor scales, when compared to children with typical neurodevelopment. The development of 46 exposed children was considered normal until the first year of life (EINSPIELER *et al.*, 2019). Other studies have reported similar results (DE FATIMA VASCO ARAGÃO *et al.*, 2016; VAN DER LINDEN *et al.*, 2016; CABRAL *et al.*, 2018; LOPES MOREIRA *et al.*, 2018; ZANCANELLI, 2018; CARDOSO *et al.*, 2019; SOARES-MARANGONI *et al.*, 2019).

In this study, symptoms of stress were investigated in the mothers, in order to know their emotional and physical states and understand how this aspect could interfere with the stimulation of their children's development. All mothers were the primary caregivers of the children. Five mothers (cases 3, 5, 7, 8 and 9) presented stress symptoms, predominantly psychological, with stress classification in the resistance phase. Three (cases 3, 5 and 8) worked and two (cases 7 and 9) was caring for the child and the house. In the resistance stage there is energy directing to resume its balance and adaptation, generating a feeling of wear. Memory difficulties, malaise, tiredness, gastric complaints, skin manifestations, changes in appetite and in blood pressure, irritability, decreased sexual desire, and excessive worry with the stressor may occur. If the body can adapt and resist the stressor properly, the process stops without leaving sequelae (LIPP, 2000). Mothers reported problems in personal, health, financial, marital and family aspects as stressors related to their psychological symptoms. From the anamnesis on aspects of child and family development and behavioral observation of mother-child interaction, satisfactory maternal stimulation was observed in all cases, except in case 4, whose mother was very young and had low socioeconomic and educational status. Studies indicate that precarious socioeconomic conditions and teenage pregnancy may interfere

with child development (HAIDAR *et al.*, 2001; GOLDENBERG *et al.*, 2005; ANAZAWA *et al.*, 2016).

This study provided important information about the clinic of asymptomatic children born to mothers with ZIKV exposure in pregnancy. However, some limitations need to be addressed. The small number of participants does not allow the generalization of the results. Patient access was difficult, since notification to health authorities is not mandatory for ZIKV infection in pregnancy with no microcephaly or other apparent changes.

Another aspect that contributed to the restricted number of participants was the requirement of inclusion and exclusion criteria, which needed to be strict to rule out the influence of other possible risk factors on neurodevelopment. Difficulties in confirming the laboratory diagnosis during the period of infection, in some cases due to lack of knowledge of the disease in the gestational period and also due to the absence of follow-up protocols at the time, thus not indicating the need to perform the exam, is a limitation of this study. Furthermore, when the mothers became aware of the need to confirm a possible infection during pregnancy, they reported difficulty in accessing laboratory tests as real-time RT-PCR in the public health system and the high cost of tests in the private health system, which prolonged the lack of confirmation of ZIKV infection. Importantly, in Brazil, laboratorial tests began to be made available on the public health system only from October 2016 (BRAZIL, 2016) after birth date of most cases. Mothers had recommendations to perform the exams, but they had economic limitations. However, all were born during the ZIKV epidemic (CAMPOS *et al.*, 2015) and all, but one asymptomatic mother, had symptoms consistent with infection during the gestational period. Thereby, evidence of previous ZIKV infection was confirmed in all mothers.

This research is ongoing to expand the sample to broaden the assessment of the evaluated children with a longitudinal appraisal. From this perspective, it is also important to monitor the evolution of cognitive development, language, motor skills and learning throughout childhood and late adolescence.

Hitherto, few studies have been published on the development of ZIKV-exposed children without pre or perinatal complications. This study is relevant considering the paucity of data regarding cognition of these children, whose development so far was supposed to be neurotypical.

5 CONCLUSION

In this paper, of the nine children evaluated by BSID-III, six had developmental changes. We hypothesized that cognitive and neurological changes observed in five children may be related to exposure to the effects of ZIKV infection on the intrauterine environment.

Therefore, the need to request for ZIKV serology in all pregnant women and include all ZIKV exposed children in longitudinal investigation protocols is fundamental to clarify how the neurodevelopmental evolution of these children will be like.

Follow-up is important to enable early stimulation once developmental delays are identified, thus enabling them to reach the full potential of the skills to be stimulated.

ETHICAL ASPECTS

This study was approved by the Ethics Committee on Research with Human Beings at Institute of Health Sciences of the Federal University of Bahia, protocol No. 2.015.503.

DECLARATION OF INTEREST STATEMENT

The authors report no conflict of interest.

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