REVIEW

Motor development of children exposed to the zika virus: systematic review

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Abstract

Objectives: to describe the motor development, in the first two years of life, of children with evidence of congenital Zika virus syndrome (CZS) at birth and of children exposed to the Zika virus (ZIKV) during pregnancy, but without evidence of CZS.

Methods: systematic review, according to the recommendations of the Preferred Reporting Items for Systematic Reviews (PRISMA). The search took place in the VHL/LILACS interface and BIREME/ PubMed interface databases until March 2020. Two researchers analyzed the quality of the studies using the Johanna Briggs Institute methodology.

Results: 21 articles were selected. Children with CZS have severe impairment of motor functions and a high prevalence of spastic cerebral palsy. At two years of life, most reached only early levels of motor development; with impaired vision, hearing, language, cognition, behavior, and social interaction. On the other hand, children exposed to ZIKV, but without evidence of CZS, are at lower risk, about 20% have late manifestations of delay and/or neurodevelopmental disorder. Variables associated with greater motor impairment are early maternal infection, preterm birth, lower head circumference, abnormal imaging, use of anticonvulsant, increasing age, arthrogryposis, epilepsy, deficits in vision, language, cognition, and lower income.

Conclusion: Most children with CZS show severe motor impairment; a small part of those exposed to ZIKV, without evidence of the syndrome at birth, have alteration in neurodevelopment. Those children should be followed in the long-term, since some manifestations may occur belatedly.

Key words *Congenital zika syndrome, Microcephaly, Motor development*

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Introduction

In Brazil, the spread of Zika virus (ZIKV) through *Aedes aegypti* mosquito was first detected in the Northeast region, and it coincided with the sudden increase of births of children with microcephaly.[1,2] The correlation of the increase of the number of microcephaly cases and maternal infection by ZIKV was proven by laboratory exams.[3,4] Initially, microcephaly was defined as the cerebral malformation most frequently related to congenital infection by ZIKV, however, it is already known that it does not occur in every case.[5]

Congenital infection by ZIKV results in a complex clinical condition denominated congenital zika virus syndrome (CZS). CZS is characterized by diverse clinical manifestations, and among the most prevalent cerebral malformations, are corpus callosum abnormalities, brain volume loss, calcifications, ventriculomegaly, cortical malformation, microcephaly (present in 55.6% to 77.8% of cases, at birth) and osteomuscular deformities.[6] Since microcephaly may be present or not, it is not the determinant element for diagnosis.[5] With regard to clinical manifestations, we highlight the impairment of motor, linguistic and cognitive functions, epilepsy, hearing and visual loss, irritability, hypertonia, dyskinesia and hyperreflexia.[5,7-9]

Between 2015 and 2020, 3,564 cases of CZS were confirmed, mostly in the Northeast region (61.9%). Of the confirmed cases, 60.6% received specialized care,[10] and since the syndrome's clinical condition is severe, complex and lead to longstanding repercussions, the proportion of children without specialized care (39.4%) is concerning.

Greater impairments in motor development are frequent in children with evidence of CZS at birth and among those with lower head circumference and severe cortical malformations.[11] Nevertheless, children with congenital infection by ZIKV, but without microcephaly and/or cerebral malformations at birth are also at risk and should have their development monitored.[8]

Motor development is a continuous process of changes in movement across life, and comes from the complex interaction between the neural and musculoskeletal systems, including cognitive and perceptive processes. It is affected by many variables, including individual aspects such as age, sex, nutrition and diseases, socioeconomic status, culture, environment factors and developed tasks. The psychometric tools of screening and assessment of motor development identified children at risk by means of the analysis of motor behaviors, postural control and functional skills.[12,13] Data quantification is an important resource to track delays, to the referral to early intervention and to help planning interventions.

There is still much to be done in regard to strengthening healthcare actions for the population to receive guidelines on prevention from ZIKV infection, prevention from vertical transmission, besides prenatal care and postpartum care. Preventive measures, early diagnosis of delay or atypical motor development, performed by means of specific screening tools and the referral to rehabilitation services mitigate the impact of the disorder in children's health.

In view of the above, the aim of this review is to analyze motor development in the two first years of life in children with CZS evidence at birth and children exposed to ZIKV during pregnancy, but without CZS evidence at birth.

Methods

Systematic review registered at the database of prospectively registered systematic reviews (PROSPERO, number CRD42020208262), developed according guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[14] Searches in the databases: BVS/interface LILACS, BIREME/interface PubMed and manual search in the reference lists of selected articles. A date filter was used to select articles published after 2015, when occurred the onset of ZIKV epidemic in Brazil, until March 2020. We used combinations of descriptors controlled in DeCS/BVS: infant development AND Zika virus; developmental disorders AND Zika virus. The combinations of descriptors of MeSH/PubMed were:psychomotor performance AND Zika virus; motor development AND Zika virus; developmental disabilities AND Zika virus. Descriptors were combined by means of AND Boolean operator,

We searched for original studies, published in the aforementioned databases and that allowed to answer the following research question: How is the motor development in the first two years of life, of children with evidence of CZS at birth and children exposed to ZIKV during pregnancy, but without scientific evidence of CZS at birth? Thus, the studied outcome was the motor development of these children in the first two years of life.

After search, duplicate titles were excluded and exclusion and inclusion criteria were applied to the others. Inclusion criteria were: 1) observational studies aiming in the description of motor development of children with CZS and/or children exposed to ZIKV during pregnancy; 2) articles that included in the sample, children with CZS manifestations (for example: laboratory evidence of congenital infection by ZIKV accompanied by microcephaly and/or other characteristic cerebral malformations and clinical manifestations of ZIKV infection); 3) articles that included in the sample, children with laboratory evidence of congenital infection by ZIKV, but without evidence of CZS at birth); 4) studies that used validated and standardized screening or assessment tools for children motor development; 5) publications quoted as reference in selected article, when met inclusion criteria.

The exclusion criteria were: 1) description of social, preventive, epidemiological and clinical aspects of ZIKV infection and CZS; 2) focus on health surveillance, protocols of intervention and treatment of children with CZS; 3) literature reviews, editorials and study protocols; 4) studies on parenting, health and wellbeing of caregivers; 5) description of clinical manifestations, malformations, hearing, language, visual and cognitive development and studies that did not use standard tools to assess development; 6) associations between *Guillain-Barré* syndrome and ZIKV; 7) studies of low methodological quality (percentage under 50% in the evaluation checklist).

The entire process of search and selection was conducted by two independent researchers. The critical evaluation of quality of studies followed the methodology of Johanna Briggs Institute (JBI).[15] Four tools were used (checklists) according to study design: checklist for case studies (eight items), checklist for case series (ten items), checklist for analytical cross-sectional studies (eight items), checklist for cohort studies (11 items). For each item, there are four options: yes, no, not clear, not applicable. We calculated the percentage of "yes" answers for each study, the "not applicable" answer was not calculated. Studies with a percentage under 50%, with risk of bias classified as high[16] were excluded.

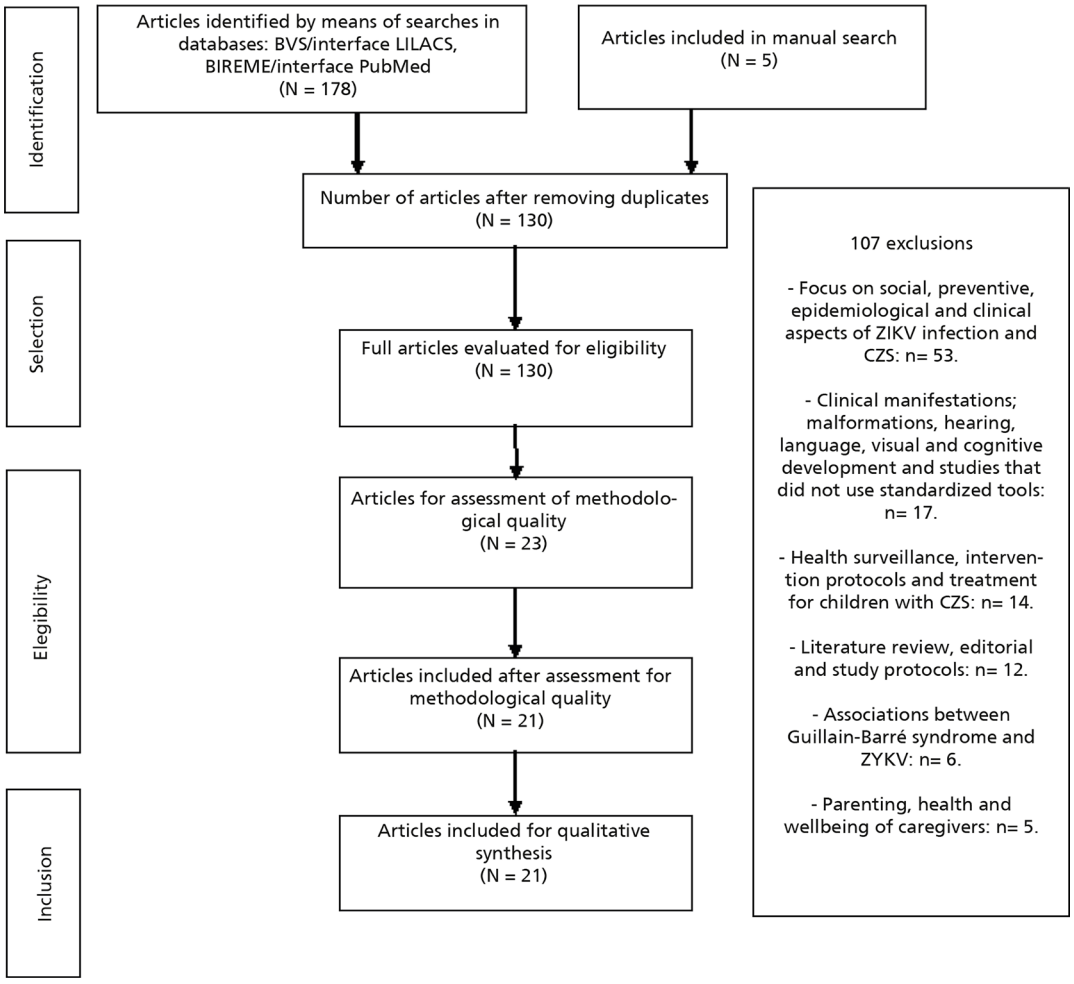
For qualitative synthesis, authors extracted data from articles by means of a form in which they filled the following information: authors, year of publication, country/state of origin if children, study type, characteristics of sample (sample size, age, CZS diagnosis or exposition to ZIKV during pregnancy), assessment tools for motor development and main results related to children motor development.

Results

178 titles were located bymeans of database search and five titles by manual search. After removing duplicates, 130 titles subject to screening remained. Of these, 107 were discarded, for meeting exclusion criteria. 23 articles then remained to be submitted for evaluation of methodological quality. Two articles were excluded for presenting scores under 50% in the Johanna Briggs Institute tool. In the end of selection, 21 articles were included for meeting inclusion criteria and having adequate methodological quality, as detailed in the flowchart (Figure 1).

Figure 1

Flowchart of PRISMA model representing the process of identification, selection, elegibility and inclusion of articles.



With regard to methodological quality evaluation, the score varied between 50% and 100%, with a mean of 82.8%, revealing good general quality. The most frequently found methodological problem in included articles was the absence of description or little clarity in the presentation of sociodemographical characteristics of participants.[8,9,17-27]

Studies selected were published between 2016 and March 2020, twenty conducted with Brazilian population and one with Colombian population.[26] Surveys conducted in Brazil included predominantly children living in the Northeast region, six studies with sample of children from Bahia state,[17,19,24,28-30] four from Pernambuco state, [18,21,23,31] three from Paraíba state[11,20,22] and two from Rio Grande do Norte state[20,23]; five were conducted in the South region, four in Rio de Janeiro state[8,9,25,27] and one in Minas Gerais[9]; two in the Midwest region, one in Mato Grosso[34] and one in Mato Grosso do Sul.[33]

Fifteen studies assessed children with CZS[11,17-25,28,29,31-33] (Table 1), three articles[26,30,34] assessed children exposed to ZIKV during pregnancy, but without confirmation or evidence of CZS at birth (Table 2) and three articles[8,9,27] assessed both children with CZS and children exposed to ZIKV, but without diagnosis of CZS at birth (Table 3). All studies included children of both genders, aged up to 32 months.

Tools used for assessment and/or classification of motor development were: Bayley-III scale, Gross Motor Function Measure (GMFM) and Gross Motor Function Classification System (GMFCS), Alberta Infant Motor Scale (AIMS), Denver Developmental Screening Test II (Denver II), Hammersmith Infant Neurological Examination (HINE), General Movements Assessment (GMA), Ages and Stages Social (ASQ-3), Warner Initial Developmental Evaluation of Adaptive and Functional Skills (WIDEA), Pediatric Evaluation of Disability Inventory (PEDI); Test of Infant Motor Performance (TIMP). Besides motor and/or functional assessment, the measured construct includes aspects related to development of socio-emotional, cognitive, language, adaptive behavior, personal-social and self-care order, as detailed in Table 4. The GMFM, GMFCS, AIMS, GMA, HINE and TIMP measure and/or classify exclusively aspects of motor development. HINE and GMA have excellent capability of predict risk of cerebral palsy.[35]

Table 1

Synthesis of articles that include children with evidence of CZS.

Author Year Country/State	Type of study Sample characteristics Assessment tool for motor development	Main results related to motor development of children
Ventura *et al.*[24] 2020 Brazil /Bahia	Longitudinal –case series Sample: 77 children. Assessed at 11, 18 and 24 months by GMFM-66. Tool: - GMFM-66 - GMFCS	At two years of age, all children had cerebral palsy diagnosis and severe motor impairment; 94.8% tetraplegia; 96.1% level V (GMFCS), mean score of 20.5% at GMFM. Two were level I at GMFCS and reached scores of 58.1 and 54.6 (GMFM) and were capable of walking without mobility device. One child, level IV, with a 36.8 score (GMFM) was capable of sit down. Little motor progress until 18 months, but the initial progress did not happen in the last assessment (2 years), 96.7% with motor development fitting 4 months or less.
Marques *et al.*[25] 2019 Brazil/Rio de Janeiro	Longitudinal - case series Sample: 39 children com CZS. Assessed at 6, 12 and 18 months. Tool: - AIMS - *Bayley*-III	AIMS: at 6 months, mean of 9.74 (equivalent to 2 to 3 months of motor age); babies with 12 months, 14.13 (equivalent to 3 to 4 months); babies with 18 months, 15.77 (equivalent to 4 to 5 months). The average score of Bayley was 10.76 (extremely low). Results of the two scales correlated in 92% (at 12 months of age). Evolution of motor development of 6 to 18 months, but children remained with severe impairment, at 12 months reached only head control, 64% with development comparable to 3 months and 89.7% presented cerebral palsy.
Melo *et al.*[11] 2019 Brazil/Paraíba	Cross-sectional - case series Sample: 59 children (27 with confirmed CZS). Mean Age: 14.7 months Tool: - GMFM-88 - GMFCS	Severe impairment in most children, but motor function was normal in 7%. 93% classified in levels IV/V of GMFCS. General score of GMFM varied from 5 to 210 (median: 18; interquartile interval 11), only four children received dimension D scores (standing) and E (walking, running and jumping). Negative correlation between motor function and severe cortical malformations and number of anticonvulsants; positive correlation between head circumference at birth with motor function and income per capita.
Carvalho *et al.*[17] 2019 Brazil/Bahia	Longitudinal - case series Sample: 82 children. Age: 4.8 and 13.2 months (*follow-up*) Tool: - *Bayley*-III - GMFCS	86.5% of levels IV and V of GMFCS. Bayley scores extremely low for cognitive function (95.1%), language (97.6%) and motor (97.6%) Correlation between cognitive score and head circumference (at birth and follow-up) and head circumference (at follow-up) with motor scores
Carvalho *et al.*[28] 2020 Brazil/Bahia	Longitudinal- case series Sample: 69 children with cerebral palsy associated with CZS. Assessment at 2 years of age. Mean Age of 24 months (23 to 32 months). Tool: - *Bayley*-III - HINE - GMFCS	Most with bilateral cerebral palsy (94.2%), spasticity (100.0%), GMFCS IV/V (92.8%), epilepsy (73.1%). Bayley-III: extremely low performance in cognition (94.2%), language (95.7%) and motor (95.7%). Average score of HINE was 21.0 (To infer at 40.0 – cerebral palsy predictor). There was correlation between head circumference at birth with cognitive, language and motor scales from Bayley, as well as the HINE. It was observed association between low HINE scores with congenital microcephaly, arthogryposis and epilepsy at the first year, abnormal electroencephalogram test

Lima *et al.*[18] 2018 Brazil/Pernambuco	Longitudinal- case series Sample: 16 children. Mean Age of 10.8 (onset) e 20.9 months (*follow-up*) Tool: - PEDI: two assessments (A1 and A2)	In A1 – self-care domain: 37.5% with delay; mobility: 100% with delay; social function: 18.8% with delay. In A2: self-care: 93.7% with delay; mobility and social function: 100%. There was a decrease in normative scores at the three PEDI domains, between the two assessments. In caregiver assistance, 100% with delay in three domains, receiving maximum or total assistance.
Wheeler *et al.*[31] 2018 Brazil/Pernambuco	Cross-sectional - case series Sample: 47 children with CZS. Mean age of 16 months (13 to 22 months). Tool: - ASQ-3	No children presented adequate development for age. Severe impairment in gross and fine motor skills (most impaired – less than half were capable of holding a small object with the hands), most with performance inferior to what was expected for six months. Only one child sat in a controlled manner and walked with support. Boys had higher score in gross motor skills. Correlation between visual disorder and fine motor skills. Lower birth weight was associated with low communication scores.
Alves *et al.*[21] 2018 Brazil/Pernambuco	Cross-sectional - case series Sample: 24 children with CZS. Mean Age of 19.9 months. Tool: - Denver II	Denver II: all children with severe development impairment. The language development was the most impaired, equivalent to 2.1 months, gross motor to 2.7 months, fine motor/adaptive to 3.1 months, personal/social to 3.4 months.
Ferreira *et al.*[20] 2018 Brazil/Paraíba e Rio Grande do Norte	Cross-sectional - case series Sample: 34 children. Mean Age 21.2 months Tool: - PEDI - GMFM-88 - Results converted into ICF qualifiers.	Brain structure with moderate disability in 55.9% and severe in 44.1%. Body functions, severe or complete disability in: mental functions of language (100%), intellectual functions (88.3%), tone (88.3%), voluntary control of members (82.3%), joint mobility (76.5%). Level of activity and participation, severe or complete disability in fine motor skills (1005), walking (70.6%); severe difficulty in basic personal interactions category (55.9%). No difficulties for familiar relationships in 88.2%
França *et al.*[32] 2018 Brazil/Rio Grande do Norte	Cross-sectional - case series Sample: 8 children with CZS (group A) and16 typical children (group B). Mean Age of 21.2 months (group A) e 20.4 (group B). Tool: - *Bayley*-III	Children of group A presented extremely low results in the cognitive domain (mean 55 ± 0) and motor domain (47 ± 2). Children of group B presented normal development in cognitive domain (100 ± 14) and motor domain (100 ± 12). Significant difference (cognitive and motor) between the groups.
Avelino *et al.*[19] 2018 Brazil/Bahia	Cross-sectional - case series Sample: 8 children. Mean Age of 1.8 years Tool: - Denver II	Comorbidities: 5 had convulsion history, 7 musculoskeletal alterations; 5 with visual impairment and 1 hearing impairment. Children were classified with development delay (Denver II), with lower development in the gross motor aspect.
Soares-Marangoni *et al.*[33] 2018 Brazil/Mato grosso do Sul	Case report Sample: 2 babies (case 1: cerebral alterations and microcephaly; case 2: no signs of CZS). Age: 4 and 12 months. Tool: - GMA/GMs - AIMS	Case 1: unquiet movements absent at 16 weeks (normal GMA) and motor development severely impaired at 12 months of age. Severe motor impairment did not allow AIMS score (unable to perform antigravity movements). Case 2: typical motor development at 12 months (AIMS).
Carvalho *et al.*[29] 2018 Brazil/Bahia	Case study - Sample: 1 case. Age: 20 months Tool: - *Bayley*-III	- Female child, presenting normal score in cognitive, language and motor development, even with microcephaly and abnormalities in neuroimaging test
Satterfield-Nash *et al.*[22] 2017 Brazil/Paraíba	Cross-sectional - case series Sample: 19 children. Mean Age of 22 months Tool: - HINE - ASQ-3	Most have severe motor alterations. In HINE: 78.94% of children presented global score under 40 (severe motor impairment) and 14 (73.67) with signs of cerebral palsy. In ASQ: 78.94% with assessment of skills under the expected for 6 months old children. 4 children had typical development
Botelho *et al.*[23] 2016 Brazil /Pernambuco	Case report Sample: 4 children. Age: three with 4 months and one with 3 months Tool: - TIMP	The four children presented atypical motor development, hyperreflexia, hypertonia and manual function disability. Three children with dysphagia, two with visual disability, two with irritability. Poor spontaneous motricity and small amplitude of movements, absence of body acquisition and maintenance in the average line, decrease in motricity and motor development.

ZIKV = Zika virus; CZS = Congenital Zika Syndrome; AIMS = *Alberta Infant Motor Scale*; ASQ-3 = *Ages and Stages Social*; *Bayley-III = Bayley Scales of Infant and Development – 3rd edition;* CIF = *International Classification of Functioning Disability and Health*; Denver II = *Denver Developmental Screening Test II*; GMA/GMs = *General Movements Assessment*; GMFM-66 = *Gross Motor Function Measure*; GMFM-88 = *Gross Motor Function Measure*; HINE = *Hammersmith Infant Neurological Examination*; PEDI = *Pediatric Evaluation of Disability Inventory*; TIMP = *Test of Infant Motor Performance*.

Table 2

Synthesis of articles that include children exposed to ZIKV during pregnancy, but without CZS diagnosis at birth.

Author Year Country/State	Type of study Sample characteristics Assessment tool for motor development	Main results related to children's motor development
Mulkey *et al.*[26] 2020 Colombia	Cohort Sample: Of 82 babies exposed to ZIKV during pregnancy, 70 children without signs of CZS were assessed. 40 assessed between 4 and 8 months (mean – 5.9 months) and 60 between 9 and 18 months (mean 13 months). Tool: - WIDEA - AIMS	Mild delays in cognitive, motor and cognitive development (WIDEA) presented decreases with age. Between 57 babies that had postnatal intracranial ultrasound, 33% presented discrete alterations, these children were more prone to experience decrease in neurodevelopment. 91% were walking independently (> 15 months of age). The AIMS scores were lower in babies with nonspecific findings in brain ultrasound.
Gerzson *et al.*[34] 2020 Brazil/Mato Grosso	Cross-sectional– case series Sample: 37 children, 17 (exposed group - ZIKV) and 20 (control). Age: 18 to 29 months (mean 26 months) Tool - Bayley-III	There was no statistical difference between the group exposed to ZIKV without microcephaly and the control group – in all three Bayley domains. In the two groups, children did not present severe impairment. In the exposed group, one child presented score under average in cognitive domain, two in language and 4 in motor.
Faiçal *et al.*[30] 2019 Brazil/Bahia	Cross-sectional– case series Sample: 29 children without cerebral lesion. Mean age: 18.2 months. Tool: Bayley-III	35% presented neurodevelopmental delay. Language delays (31%), cognitive (13.8%) and motor (3.4%). Language impairment: 3.4% severe (score -3 SD), 3.4% moderate (-2 SD), 24.1% mild (-1 SD to -2 SD); cognitive: 13.8 mild; motor: 3.4 mild. Language was the most impaired domain.

Table 3

Synthesis of articles that include both children with CZS evidence at birth, and children exposed to ZIKV during pregnancy, but without CZS diagnosis at birth.

Nielsen-Saines *et al.*[8] 2019 Brazil / Rio de Janeiro	Cohort Sample: 216 children (follow-up from 7 to 32 months, mean 18 months), only 8 children with microcephaly) Tool: - HINE andBayley-III (216 children) - Bayley-III (146 assessed children)	Among 216 children evaluated by HINE and Bayley scales, 71.3% had normal development and 28.7% had delay. Between 146 children assessed by Bayley, 31.5% presented low performance and/or signs of abnormality in development, 28.1% presented performance below average (score between 1 and -2 SD) and 12.3% had performance significantly below average (lower than -2 SD). The language development was the most affected, with 34.9% scoring below -1 SD. 9.6% with cognitive delay (below -1 SD) and 16.4% motor delay (below -1 SD). Three children developed autism spectrum disorder. Aspects associated with worse results were early maternal infection, preterm birth, male gender and abnormal visual test.
Einspieler *et al.*[9] 2019 Brazil /Rio de Janeiro e Minas Gerais	Cohort Sample (111 exposed to ZIKV, 333 controls). Among the 111 exposed, 76 did not have microcephaly and 35 had microcephaly. Assessment at 9 to 20 weeks of life and at 12 months. Tool: - GMA/GMs (9 to 20 weeks) - Bayley-III (12 months) - GMFCS	The 333 children from the control group presented normal motor development. GMA/GMs: children exposed to ZIKV and without microcephaly, 84.2% (64/76) presented normal spontaneous movements and 15.8% (12/76) abnormal or absent movements (fidgety), among those with microcephaly 100% (35) absent movements (fidgety). 17.9% (10/56) of children without microcephaly and ZIKV positive presented development delay (Bayley) at 12 months (seven from 10 children were identified by GMA, positive predictive GMA value was 78%). Motor impairment was higher between the 35 children with microcephaly by ZIKV, they were not able to maintain antigravity postures of head and body; 79.4% had epilepsy; the lower the head circumference, the more abnormal the movement standards.
Moreira *et al.*[27] 2019 Brazil /Rio de Janeiro	Cohort Sample: 182 children. Age: between 12 and 18 months Tool: - 49 of 182 (26.9%): hearing exams - 112 of 182 (26.9%): visual exams - 115 of 182 (63.2%): neuroimaging - 104 of 182 (57.1%): Bayley-III scale - 94 of 182 (51.6%): neuroimaging and Bayley-III	No microcephaly case was detected and findings in neuroimaging were normal in 44 children (47%). Of the 94 children assessed by Bayley-III and neuroimaging, 63% had normal scores, 26% scores between -1 and -2 SD, 12% scores below -2 SD. Of the 58 children with normal neuroimaging, 47% did not have delay (Bayley- normal); 13.8% with scores between -1 and -2 SD; 2.1% with scores below -2 SD. Of the 35 children with abnormal neuroimaging results, 16% had normal scores in Bayley, 12% with scores under -1 and -2 SD and 10% with scores under -2 SD. There is association of normal neuroimaging results with higher Bayley scores. However, normal neuroimaging did not predict development delay.

ZIKV = Zika vírus; CZS = congenital Zika syndrome; SD = standard deviation; AIMS = *Alberta Infant Motor Scale*; *Bayley*-III = *Bayley Scales of Infant and Development – 3nd edition*; GMFCS = *Gross Motor Function Classification System*; GMA/GMs = *General Movements Assessment*; HINE = *Hammersmith Infant Neurological Examination*; WIDEA = *Warner Initial Developmental Evaluation of Adaptive and Functional Skills.*

Table 4

Description of tools used for assessment and/or classification of motor development.

Tool	Assessed/classified aspects	Author	Title
Bayley Scales of Infant and Development – 3nd edition (*Bayley*-III)	Evaluates infant development in five domains: cognitive, language, motor, socio-emotional and adaptive behavior.	Nielsen-Saines *et al.*[8]	Delayed childhood neurodevelopment and neurosensory alterations in the second year of life in a prospective cohort of ZIKV - exposed children
		Einspieler *et al.*[9]	Association of infants exposed to prenatal Zika virus infection with their clinical, neurologic, and developmental status evaluated via the general movement assessment tool
		Carvalho *et al.*[28]	Cerebral palsy in children with congenital Zika syndrome: a 2-year neurodevelopmental follow-up
		Carvalho *et al.*[17]	Clinical and neurodevelopmental features in children with cerebral palsy and probable congenital Zika
		Carvalho *et al.*[29]	Congenital Zika virus infection with normal neurodevelopmental outcome, Brazil
		Marques *et al.*[25]	Children born with congenital zika syndrome display atypical gross motor development and a higher risk for cerebral palsy
		Gerzson *et al.*[34]	Neurodevelopment of nonmicrocephalic children, after 18 months of life, exposed prenatally to Zika virus
		Moreira *et al.*[27]	Neurodevelopment in infants exposed to zika virus in utero
		França *et al.*[32]	Growth and development of children with microcephaly associated with congenital Zika virus syndrome in Brazil
		Faiçal *et al.*[30]	Neurodevelopmental delay in normocephalic children with in utero exposure to Zika virus
Gross Motor Function Measure (GMFM-66)	Measurement of gross motor function in palsy (motor performance in five dimensions: laying and rolling; sitting down; crawling and kneeling; standing, running and jumping).	Ventura *et al.*[24]	Early gross motor development among Brazilian children with microcephaly born right after Zika virus infection outbreak
Gross Motor Function Measure (GMFM-88)	Measurement of gross motor function in palsy (motor performance in five dimensions: laying and rolling; sitting down; crawling and kneeling; standing, running and jumping).	Melo *et al.*[11]	Motor function in children with congenital Zika syndrome
		Ferreira *et al.*[20]	Functioning and disability profile of children with microcephaly associated with congenital Zika virus infection
Gross Motor Function Classification System (GMFCS)	Classifies gross motor function of children with cerebral palsy in five levels: level I are mildly affected (marching prognosis), at level V the impairment is severe (use of wheelchair for locomotion).	Melo *et al.*[11]	Motor function in children with congenital zika syndrome
		Ventura *et al.*[24]	Early gross motor development among Brazilian children with microcephaly born right after Zika virus infection outbreak
		Carvalho *et al.*[28]	Cerebral palsy in children with congenital Zika syndrome: a 2-year neurodevelopmental follow-up
		Carvalho *et al.*[17]	Clinical and neurodevelopmental features in children with cerebral palsy and probable congenital Zika
		Einspieler *et al.*[9]	Association of infants exposed to prenatal Zika virus infection with their clinical, neurologic, and developmental status evaluated via the general movement assessment tool
Denver Developmental Screening Test II (Denver II)	Tool for early screening of development conditions, assessing four areas/categories: gross motor, fine adaptive motor, language and personal-social.	Avelino *et al.*[19]	Analysis of neuropsychomotor development in children with congenital Zika syndrome: a cross-sectional study
		Alves *et al.*[21]	Neurodevelopment of 24 children born in Brazil with congenital Zika syndrome in 2015: a case series study
Alberta Infant Motor Scale (AIMS)	Evaluates the sequence of motor development and control of antigravity muscles, considers four subscales: prone, supine, sitting and standing.	Marques *et al.*[25]	Children born with congenital Zika syndrome display atypical gross motor development and a higher risk for cerebral palsy
		Soares-Marangoni *et al.*[33]	General movements and motor outcomes in two infants exposed to Zika virus: brief report
		Mulkey *et al.*[26]	Neurodevelopmental abnormalities in children within utero Zika virus exposure without congenital Zika syndrome
General Movements Assessment (GMA)	Assessment of general movements. Predictive assessment for cerebral palsy detection.	Einspieler *et al.*[9]	Association of infants exposed to prenatal Zika virus infection with their clinical, neurologic, and developmental status evaluated via the general movement assessment tool
		Soares-Marangoni *et al.*[33]	General movements and motor outcomes in two infants exposed to Zika virus: brief report

Social and Ages and Stages Social (ASQ-3)	Evaluates development in five dimensions communication, gross motor, fine motor, problem solving and personal/social.	Wheeler *et al.*[31]	Skills attained by infants with congenital Zika syndrome: Pilot data from Brazil
		Satterfield-Nash *et al.*[22]	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
Hammersmith Infant Neurological Examination (HINE)	Predictive assessment for cerebral palsy detection. Assesses the domains: posture and tone, reflexes, movements, abnormal standards and signs, orientation and behavior.	Carvalho *et al.*[28]	Cerebral palsy in children with congenital Zika syndrome: a 2-year neurodevelopmental follow-up
		Satterfield-Nash *et al.*[22]	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
		Nielsen-Saines *et al.*[8]	Delayed childhood neurodevelopment and neurosensory alterations in the second year of life in a prospective cohort of ZIKV - exposed children
Pediatric Evaluation of Disability Inventory (PEDI)	Measures functional skills in three dimensions: self-care, mobility and social function; considers the help provided by caregivers.	Lima *et al.*[18]	Analysis of the functional performance of infants with congenital Zika syndrome: a longitudinal study
Test of Infant Motor Performance (TIMP)	Motor performance and posture control in the categories: sustaining posture; recovering posture, transition between postures, integration of dynamic postures.	Botelho *et al.*[23]	Presumed congenital infection by Zika virus: findings on psychomotor development - a case report
Warner Initial Developmental Evaluation of Adaptive and Functional Skills (WIDEA)	Evaluates skills in the following domains: self-care, mobility, communication and social cognition.	Mulkey *et al.*[26]	Neurodevelopmental abnormalities in children within utero Zika virus exposure without congenital Zika syndrome

Studies that included children with CZS evidence

In the 15 studies that assessed children with CZS evidence, authors highlighted that the inclusion criteria in thesample were mainly laboratory exams that verified ZIKV congenital infection, microcephaly and/or cerebral congenital manifestations and clinical manifestations typical of ZIKV infection. Children were aged up to 32 months, the study[29] with the smaller sample described a single case and that with the greatest sample included 82 children.[17] The total of assessed children was 487, but the methodological and authorial similarity indicates that at least 2 studies used part of the same sample group.[17,28] Five studies had prospective longitudinal model.[17,18,24,25,28] Five surveys used Bayley-III scale,[17,25,28,29,32] the authors highlighted the high proportion of children with extremely low mean scores in the cognitive, motor and language domains. Studies that included more than one development assessment tool – AIMS and Bayley-III,[25] Bayley-III and HINE,[28] HINE and ASQ-3,[22] AIMS and GMA/GMs[33] - concluded that results were similar and/or correlated to the associated use of scales confirmed low motor development and evolution of children.

Among the main results, we highlight high frequency of cerebral palsy, severe global motor development, bilateral spasticity (quadriplegia), most children were classified in levels IV or V of GMFCS,[11,17,21,22,24,25,28] even at two years old, reached only initial levels of motor control, which are the control of the had in prone position and being able to sit with support. Circa 73.67% to 100% of the sample presented signs of cerebral palsy and spasticity; [22,24,25,28] 86.5% to 92.8% were classified in levels IV and V of GMFCS.[11,17,28] On the other hand, 7% to 21% had typical development,[11,22] two children were classified in level I and were capable of walking without auxiliary device and one child, level IV, was able to sit down.[24] There is also the report of a child of twenty months of life with congenital microcephaly and abnormalities at the neuroimaging test, but with normal scores in the cognitive, motor and language domains, measured by Bayley-III scale.[29]

An evaluation with 34 children was converted in qualifiers of the International Classification of Functioning, Disability and Health (ICF) and demonstrated high proportion of children with severe or complete disorder in intellectual and language functions, muscle tone, joint mobility, voluntary movement control, fine motor skills and walking.[20] A study with PEDI inventory highlighted severe functional impairment, resulting in need for maximum or total assistance from caregivers, in the domains of self-care, mobility and social function.[18]

Studies that included children exposed to ZIKV during pregnancy, but without evidence of CZS at birth

Three articles included children exposed to ZIKV during gestation, however, without CZS diagnosis at birth.[26,30,34] 128 children were assessed, aged between four to 29 months. One study had longitudinal follow up and used AIMS and WIDEA to evaluate development,[26] two cross-sectional studies used Bayley-III scale.[30,34]

Most children exposed to ZIKV in pregnancy that were born without microcephaly or alterations in brain imaging tests did not show delay, 91% were walking without support at 15 months of age. However, 33% of children in the follow up presented ultrasound with discrete alterations and were more subject to delays in the first 18 months of live.[26] A study[34] that compared 17 children exposed to ZIKV and without microcephaly with 20 non-exposed children, did not show difference between the groups. In the exposed group, one child showed a score under mean average in the cognitive domain, two in language and four in motor function.[34] Among 29 exposed children without cephalic lesion, 31% of language delay was identified, as well as 14% in cognition and 3% in motor function.[30]

Studies that included both children with CZS evidence at birth and exposed children without CZS evidence

Three studies followed the development of both children exposed to ZIKV in pregnancy and with evidence of CZS (microcephaly and/or specific alteration in imaging tests), and those exposed, but without CZS evidence.[8,9,27] The methodological and authorial similarity indicates that these studies used part of the same sample group. Bayley-III scale was used in the three cohorts, one survey included HINE scale[8] and another, the GMA/Gms and GMFCS.[9]

A follow-up study included 216 children exposed to ZIKV, 8 with microcephaly, at two years 71.3% had normal development and 28.7%, delay. Language development was the most affected, followed by motor and cognitive.[8] A follow-up study until 12 months of age, of 444 children (111 exposed, 56 without microcephaly and ZIKV positive, 35 with microcephaly, 333 controls) indicated that 84.2% of children without microcephaly presented normal spontaneous movements and 15.8%, abnormal or absent movements. Every child with microcephaly presented abnormal or absent movements, bilateral spasticity and difficulty in maintaining postures against gravity. Ten children without microcephaly presented development delay (Bayley-III) at 12 months, of these, seven were identified by GMA/GMs at three months, reassuring the importance of this tool for early screening and detection of neurological disorders that lead to motor impairment.[9]

Besides motor delay, children exposed to ZIKV are subject to delay in language and cognitive functions, visual and hearing impairments.[27] Among postural alterations present in children exposed to ZIKV, and more frequent in those with microcephaly, we highlight: head out of average line, postural asymmetry, neck and or/thorax hyperextension, limbs in extension, fingers in extension and abduction, lack of variety of movements and postures.[9]

Discussion

The systematic review demonstrated that children with congenital ZIKV infection, mainly those with CZS evidence at birth, presented severe motor impairment and minor evolution across the years. Even at two years of life, most of them achieved only the initial levels of gross motor development. The major difficulty is to assume high postures that demand control against gravity, since motor coordination and head and body control are little developed or absent. The most impaired motor functions include activities in the sitting, standing and walking postures[9,21,24,25,31] and the motor repertory is poor.[8,18,21,23,28] There is high prevalence of cerebral palsy with bilateral spasticity, epilepsy, persistence of primitive reflexes, poor balance reactions, extension spasms and neuromusculoskeletal deformities and abnormal posturing.[8,11,22,24,25,28]

Among frequent neuromusculoskeletal disorders in children with CZA are: spasticity, hyperreflexia, spasms, clonus,[17,21,24,28,31] persistence of primitive reflexes, dyskinesia, absent or abnormal posture reactions,[9,18,21,23,25,28] musculoskeletal deformities,[9,17,19,28,31] hip dislocation,[18] epilepsy/convulsions[9,11,17-19,21,22,24,25,28,31] and growth impairment.[32] The broad involvement of several body structures reverberates in posture and atypical and poorly-varied movements, asymmetry and severe motor impairment. Motor alterations and epilepsy are among the most common disorders in children with CZS and need to be early identified so that they can meet the criteria of clinical assessment, followed by early referral to intervention strategies.[7]

The disorders are extensive and complexand involve several functions, such as cognitive, speech and language, [8,21,22,26,28,31], hearing,[8,17-19,21,22,25,28,32] visual [8,18,19,21-23,31,33] social[18,21,22,26,31] cognition/learning,[8,17,20,26,28,31,32] emotional,[22] behavioral (irritability)[23], deglutition/feeding[18,24], breathing[18,22,23] and sleep.[22,31] We highlight that both gross and fine motor development are strongly related to cognitive and language disorders.[36]

Motor disabilities bring severe consequences such as: dysphagia, structured musculoskeletal deformities, poor sensorial, emotional and environmental exploration, with consequent impairment in the other areas of neurodevelopment. Limitations on basic functions such as eating and self-hygiene imply permanent need for care and assistance.[31]

With regard to follow-up across time, the motor development of children with CZS presented decline with the increase of age,[18,26] or even with small progress, the impairment remained severe.[24,25] Analyses demonstrated association of motor development with cortical malformations or administration of anticonvulsant drugs,[9,11,27] congenital microcephaly,arthrogryposis, epilespy and abnormal imaging test.[26,28] Lower head circumference is associated with greater impairment of motor,[9,11,17,28] cognitive[9,17,27,28] and low income *per capita*.[11] Greater impairment in development is associated with early maternal infection, preterm birth and abnormal eye exam.[8] Association between visual disorder and higher impairment of fine motor skills; low birthweight is associated with lower communication scores[31] In regard of the relationship of the children's gender and severity of neuropsychomotor impairment, two studies[8,31] bring diverging results. Nielsen-Saines *et al*.[8] highlight that the development was more affected in male children, while Wheeler *et al*.[31] described how boys presented better gross motor skills. These findings reinforce the importance of further analyses that investigate risks related to gender.

Children that were born without microcephaly and normal neuroimaging (or subtle alterations) may evolve with delays in development and should be followed in the long-term, since impairment manifestations may occur late. Although a high proportion of babies exposed to ZIKV without microcephaly develop normally, 15.8%[9] to 33%[26] will have atypical development.

A positive aspect highlighted by one study,[8] is the fact that children with lower neurological impairment, which suffered negative effects of virus exposition at the first months of life may have normal performance in late assessments. Two children who had microcephaly at birth reached normal head circumference and development at the second year of life. On the other hand, three children, without microcephaly, developed autism spectrum disorder.[8] One child, with normal head circumference at birth, developed secondary microcephaly and presented abnormal standards in movements.[9]

Studies pointed the association between births of neonates with microcephaly by ZIKV and bad life conditions, evidencing that socioeconomic factors also played a role in ZIKV epidemic in Brazil and may have contributed to a higher distribution of cases in economically vulnerable areas in the Northeast of the country.[37,38] Low income families with many family members have greater chance of having a child with ZIKV congenital infection, on the other hand, higher maternal schooling seem to be a protective factor. There is also consistent relation between the delay in language, motor and cognitive development and unfavorable socioeconomic indicators.[39]

The severe motor impairment in children with CZS is certainly a public health problem and higher care should be provided to families in situation of socioeconomic vulnerability. Considering that neurodevelopmental disorders are permanent and tend to get worse across time, demanding permanent care, high financial costs and overloading families even more.

Even in face of this challenging scenario, we highlight positive aspects. Challenges are encouraging scientific research in Brazil, valorizing competence and effort from Brazilian researchers, and strengthening relationships and international scientific partnerships, allowing the achievement of social rights and expanding knowledge related to assessment and healthcare for people with disabilities. It should be also considered the possibility of a higher visibility and opportunity to expand prevention and rehabilitation strategies to people who have other neurodevelopmental disorders.

As limitations related to results of this review, we mention the heterogeneity of definition of criteria for sample composition, mainly concerning evidence of ZIKV congenital infection and definition of CZS evidence. There is little information on results of clinical, laboratory and/or image tests; and risk of problems in medical records registries. The main parameter for CZS definition in children with congenital ZIKV infection was the presence of microcephaly and/or other cerebral malformations (among them, intracranial calcifications, ventriculomegaly, and cerebral atrophy). However, it is known that microcephaly might not be the best parameter to detect children affected by CZS, since it may not be present at birth, nor follow other findings that evidence CZS, or have further onset.[6] Accordingly, there is lack of standardization in terminology and protocols for CZS diagnosis. It should be also considered that parameters to identify babies with suspected microcephaly and protocols to assess CZS have been modified by the World Health Organization.[5]

It should be also considered that even screening, assessment and classification tools for development have been translated, adapted and validated for use in the study population, and they were developed and standardized mainly in the United States and Canada, countries in which the normative sample was established. A systematic review demonstrated limitedvalidity of these tests in different cultures than those in which the normative sample was established.[13] Moreover, there still exists little or no description at all about the expertise of researchers for the application of tools and about the standardization of assessment and interpretation of results.

Considering the impact of the ZIKV epidemic and its repercussions in the development of children affected by CZS and lives of families, it draws attention to the fact that we were not capable of finding more studies aiming at the assessment of motor development of the affected population. We question whether it occurred because of the fact of being an epidemiological event that affected a specific demographic area (South America, Brazil).

As final considerations, children with CZS present severe impairment in motor functions, even at two years of life, and most children only were able to reach the initial stages of gross motor development. There was high prevalenceof bilateral spastic cerebral palsy, with higher proportion of children classified at levels IV and V of GMFCS, impairment of other functional areas such as sight, hearing, language, cognition, behavior and social interaction. On the other hand, children exposed to ZIKV, but without CZS evidence at birth, are at lower risk, 15.5% to 33% develop with delay and/or abnormality of neurodevelopment, impairing mainly language functions. Finally, the results of this review evidenced that children exposed to ZIKV, with or without CZS, should have their global development monitored in the long-term, since some manifestations may have late onset.

Children should have their psychomotor development assessed across the years, preferably with standardized tests, and those with suspected delay or neurodevelopmental abnormality should be referred to early intervention with a specialized team. The approach should be early and multiprofessional, comprising biopsychosocial aspects, with strategies of prevention for new cases and mitigation of harms. We highlight the importance of implementing criteria for terminology and early diagnosis for both congenital infection and CZS, besides further longitudinal studies and implementation of intervention strategies aiming for better functionality and social participation of the affected population. It is also necessary to include families in the social and healthcare programs, since the demands required by children affected by CZS are broad and longstanding.

Author's contribution

Ribeiro MFM and Queiróz KBP participated in the conceptualization and study design, performed the search, selection and synthesis of articles. Ribeiro MFM and Prudente COM contributed to the data synthesis and final reviews of the manuscript. The authors approved the final version of the manuscript and declare no conflict of interest.

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