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Original articles

Characterization of linguistic development of children affected by congenital Zika virus syndrome as compared to typically developing peers

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ABSTRACT

Purpose: to describe the development, focusing on language, of children affected by congenital Zika syndrome and compare it with that of typically developing children.

Methods: a quantitative, observational, cross-sectional, case-control study. Data from the group of children with congenital Zika virus syndrome (case) were matched for sex and age with data from the group of typically developing children without comorbidities (control). The research included 20 parents/guardians of the children in the case group and 20 parents/guardians of the children in the control group, using interview as an adapted instrument. The data underwent descriptive and inferential statistical analysis, through association tests and comparison of means, with the significance level set at 5%.

Results: there was a statistical difference in motor, auditory, and language development between the groups, according to the parents' perception.

Conclusion: based on the caregivers' reports, most of the case group communicated non-verbally through babbling, shouting, and eye contact, whereas the minority communicated through dialogue, understood simple orders, and performed imitative behaviors, symbolic play, and shared attention. On the other hand, the control group communicated through complex sentences constructed into narratives.

Keywords: Zika Virus Infection; Microcephaly; Language; Socialization

INTRODUCTION

Congenital Zika virus syndrome (CZS) consists of congenital anomalies associated with transplacental Zika virus (ZIKV) infection, including intracranial calcifications, severe brain abnormalities, a wide range of clinical signs, and microcephaly[1]. Prenatal exposure to ZIKV increases the risk of severe microcephaly in infants with a varied degree of severity, prognosis, and damage to the central nervous system[2].

The number of children born with microcephaly unexpectedly increased in October 2015, initially in Pernambuco and later in other Northeastern Brazilian states, following the confirmation of autochthonous transmission of ZIKV fever in Brazil[3]. Pernambuco used to record 10 cases of microcephaly on average per year. However, 141 cases of microcephaly were detected from the beginning until November 11, 2015, in 44 of that state's 185 municipalities[4]. The Ministry of Health reported in a special notification protocol in the second half of 2015 more than 3,000 suspected cases of microcephaly (approximately 20 cases per 10,000 live births), which suggests an increase in the prevalence of births[5].

Measures to prevent this disease must be effective and safe, fighting vector transmission and, consequently, the numerous associated sequelae – which can compromise child development in its various domains (motor, sensory, cognitive, and linguistic)[6], directly impacting their communication and quality of life.

A literature review[6] on Zika carried out in online databases (MEDLINE and EMBASE) from the beginning of the outbreak until September 30, 2016, showed that CZS has a recognizable pattern of structural anomalies and functional deficiencies secondary to central ones and damage to the nervous system. Some of this syndrome characteristics, such as cognitive, sensory, and motor deficiencies, are shared by other congenital infections, manifested, for instance, as severe microcephaly with partially collapsed skull, subcortical calcifications, macular scars, retinal pigment epithelium mottling, congenital contractures, early hypertonia, and symptoms of extrapyramidal involvement.

Given these neurological impairments and the reports in the literature[4-6] of language, cognition, and socialization deficits, it is necessary to know these children's development and compromised skills, including eye contact, vocalizations, gestures, expressive and receptive oral language, lexicon, ability to point or use indicative gestures, shared attention, and so forth.

Hence, this article aimed to describe the development of children affected by CZS, focusing on their language, and comparing it with that of typically developing children.

METHODS

This study was approved by the Human Research Ethics Committee of the Department of Health Sciences of the Universidade Federal da Paraíba, PB, Brazil, under evaluation report number 4.101.795 and Certificate of Presentation for Ethical Appraisal (CAAE): 32451820.0.0000.5188.

This quantitative, observational, cross-sectional, case-control study paired data from the parents of children with CZS (case group) with those of typically developing children without comorbidities (control group), using the specific sex and age (year and month) criteria. The control group was selected as recommended by speech-language-hearing pathologists who accompanied children in their homes whose development was as expected for their age group. The researchers explained the study objectives to the children's parents/guardians, who signed an informed consent form. The participants' identities remained confidential, complying with human research ethical recommendations.

Data were collected in a research laboratory, with the participation of 20 parents/guardians of children in the case group and 20 parents/guardians of children in the control group.

The main researcher (speech-language-hearing pathologist) collected data in June, July, and August 2021. The parents/guardians answered a structured interview in meetings lasting about 20 minutes. The interview investigated data on pregnancy, birth, early childhood, language acquisition, and hearing development and was adapted from the medical history survey by Prof. Dionísia Cusin Lamônica[7] and authors Hage and Pinheiro[8]. The data were tabulated in a 2016 Microsoft Office Excel spreadsheet and then exported to the Statistical Package for the Social Sciences (SPSS) 25.0 program.

The study analyzed the following: data on pregnancy and birth, early childhood difficulties, motor, audiological, and language characterization, oral language acquisition, and the relationship between birth and lexicon.

Descriptive and inferential statistical analyses were performed with SPSS 25.0 software. Absolute and relative frequency measures were extracted for descriptive analysis, in addition to measures of central tendency (e.g., mean and standard deviation), allocated in the Tables. The Pearson´s chi-square test was performed to verify whether there was any association between the categorical variables of the study. The Mann-Whitney test was used to compare the quantitative samples of the two groups. Significance was set at 5%.

RESULTS

The research participants, 50% males and 50% females, were 4 years and 4 months to 5 years and 9 months old.

The caregivers' information shows that the groups were homogeneous for most sample categorization, pregnancy, and birth variables, as seen in Table 1. There was a significant difference in birth weight, as four children in the case group and none in the control group were born with low birth weight.

Table 1. Characterization of the samples with data on pregnancy and birth compared between the groups

Variables		CASE GROUP		CONTROL GROUP		p-value
		n	%	n	%	
Prenatal care	No	1	100.0%	0	0.0%	0.500
	Yes	19	48.7%	20	51.3%	
Good health during pregnancy	No	0	0.0%	0	0.0%	1.0
	Yes	20	50.0%	20	50.0%	
Gestational age	Preterm newborn	1	100.0%	0	0.0%	0.250
	Full-term newborn	19	50.0%	19	50.0%	
	Post-term newborn	0	0.0%	1	100.0%	
Sex	Females	7	50.0%	7	50.0%	0.629
	Males	13	50.0%	13	50.0%	
Birth weight	Low weight	4	100.0%	0	0.0%	0.035*
	Adequate weight	16	44.4%	20	55.6%	
Birth complications	No	17	45.9%	20	54.1%	0.072
	Yes	3	100.0%	0	0.0%	
ICU stay	No	20	50.0%	20	50.0%	1.0
	Yes	0	0.0%	0	0.0%	
Infant hearing screening test	No	1	100.0%	0	0.0%	0.349
	Passed	18	47.4%	20	52.6%	
	Failed	1	100.0%	0	0.0%	
Current age	53 months	1	50.0%	1	50.0%	1.0
	63 months	1	50.0%	1	50.0%	
	64 months	4	50.0%	4	50.0%	
	65 months	4	50.0%	4	50.0%	
	66 months	2	50.0%	2	50.0%	
	67 months	6	50.0%	6	50.0%	
	68 months	1	50.0%	1	50.0%	
	71 months	1	50.0%	1	50.0%	
Speech-language-hearing follow-up	No	8	100.0%	0	0.0%	<0.001*
	Once a week	4	100.0%	0	0.0%	
	Twice a week	8	100.0%	0	0.0%	
	Not required	0	0.0%	20	100.0%	

Variables		CASE GROUP		CONTROL GROUP		p-value
		n	%	n	%	
Medication use	No	4	16.7%	20	83.3%	<0.001*
	Yes	16	100.0%	0	0.0%	
Breastfeeding	Few days	3	75.0%	1	25.0%	0.099
	2 months	1	100.0%	0	0.0%	
	3 months	3	100.0%	0	0.0%	
	4 months	0	0.0%	0	0.0%	
	5 months	0	0.0%	1	100.0%	
	6 months	10	41.7%	14	58.3%	
	7 Mixed	0	0.0%	3	100.0%	
	8 only formula	3	75.0%	1	25.0%	

Source: The authors, 2021.
Captions: n = absolute frequency; % = percentage frequency; ICU = intensive care unit
Pearson's chi-square test; significance at $p < 0.05$.

There was a difference between the groups in speech-language-hearing follow-up, attended only by children in the group. There was also a difference in controlled medications, used by 16 children in the case group but none in the control group.

Data in Table 2 show that most difficulties were similar in the case and control groups, except for the fact that children with CZS cried more frequently and had seizures.

Table 2. Main early childhood difficulties faced by children in the case and control groups

Variables	CASE				CONTROL				p-value
	NO		YES		NO		YES		
	n	%	n	%	n	%	n	%	
Weak suction	17	48.6%	3	100.0%	20	51.4%	0	0.0%	0.073
Family problems	20	50.0%	0	0.0%	20	50.0%	0	0.0%	1.0
Difficulty gaining weight	18	47.4%	2	100.0%	20	52.6%	0	0.0%	0.244
Intestinal problems	20	50.0%	0	0.0%	20	50.0%	0	0.0%	1.0
Vomiting	20	50.0%	0	0.0%	20	50.0%	0	0.0%	1.0
Colic	20	51.3%	0	0.0%	19	48.7%	1	100.0%	0.500
Seizures	16	44.4%	4	100.0%	20	55.6%	0	0.0%	0.035*
Weak cry	19	48.7%	1	100.0%	20	51.3%	0	0.0%	0.500
Excessive crying	10	33.3%	10	100.0%	20	66.7%	0	0.0%	<0.001*
Fussy baby	20	51.3%	0	0.0%	19	48.7%	1	100.0%	0.500
Respiratory problems	19	48.7%	1	100.0%	20	51.3%	0	0.0%	0.500
Sleep problems	17	48.6%	3	100.0%	20	51.4%	0	0.0%	0.073
Heart problems	20	50.0%	0	0.0%	20	50.0%	0	0.0%	1.0

Source: The authors, 2021. Pearson's chi-square test; significance at $p < 0.05$
Captions: n = absolute frequency; % = percentage frequency.

According to data in Table 3, there was greater developmental impairment in children with CZS (case group), regarding motor and language difficulties. Most children in the case group communicated with their caregivers using elementary skills, such as shouting, vowel sounds, and gazing – unlike those in the control group, who communicated with sentences with complex syntax forming narratives.

Table 3. Motor, audiological, and language characterization of the case and control groups and comparison between the groups

Variables	CASE				CONTROL				p-value
	NO		YES		NO		YES		
	n	%	n	%	n	%	n	%	
Motor difficulties	1	4.8%	19	100.0%	20	95.2%	0	0.0%	<0.001*
Startled reaction	1	50.0%	19	50.0%	1	50.0%	19	50.0%	1.0
Audiological assessment	6	23.1%	14	100.0%	20	76.9%	0	0.0%	<0.001*
Shouting	8	28.6%	12	100.0%	20	71.4%	0	0.0%	<0.001*
Vowel sounds	10	33.3%	10	100.0%	20	66.7%	0	0.0%	<0.001*
Babbling	18	47.4%	2	100.0%	20	52.6%	0	0.0%	0.224
Functional words	16	44.4%	4	100.0%	20	55.6%	0	0.0%	0.053
Telegraphic sentences	19	48.7%	1	100.0%	20	51.3%	0	0.0%	0.500
Gazing/eye contact	8	28.6%	12	100.0%	20	71.4%	0	0.0%	<0.001*
Gestures	16	44.4%	4	100.0%	20	55.6%	0	0.0%	0.053
Jargon	19	48.7%	1	100.0%	20	51.3%	0	0.0%	0.500
Sentences complete syntax	18	47.4%	2	100.0%	0	0.0%	20	52.6%	0.224

Source: The authors, 2021. Pearson's chi-square test; significance at $p < 0.05$.
Captions: n = absolute frequency; % = percentage frequency.

The caregivers also reported that children in the case group underwent audiological assessment, whereas none in the control group had such a need.

The data in Table 4 show a statistically significant difference between children in the case and control groups in the following aspects: initiating dialogue, obeying simple orders, imitative behaviors, symbolic play, and shared attention – the group of children with CZS had lower percentages than the group of typically developing ones.

Table 4. Continued: Language characterization and comparison between groups

Variables	CASE						CONTROL						p-value
	NO		YES		NA		NO		YES		NA		
	n	%	n	%	n	%	n	%	n	%	n	%	
Dialogue	1	100%	3	13.0%	16	100%	0	0.0%	20	87.0%	0	0.0%	<0.001*
Echolalia	20	50.0%	0	0.0%	0	0.0%	20	50.0%	0	0.0%	0	0.0%	1
Simple orders	15	100%	5	20.0%	0	0.0%	0	0.0%	20	80.0%	0	0.0%	<0.001*
Imitation	19	86.4%	1	5.6%	0	0.0%	3	13.6%	17	94.4%	0	0.0%	<0.001*
Symbolic play	17	100%	3	13.0%	0	0.0%	0	0.0%	20	87.0%	0	0.0%	<0.001*
Stereotypy	17	45.9%	3	100%	0	0.0%	20	54.1%	0	0.0%	0	0.0%	0.115
Shared attention	16	88.9%	4	18.2%	0	0.0%	2	11.1%	18	81.8%	0	0.0%	<0.001*

Source: The authors, 2021. Pearson's chi-square test; significance at $p < 0.05$.
Captions: NA = not asked parents/guardians; n = absolute frequency; % = percentage frequency.

Table 5 shows that most children in the case group had not uttered their first words, and a minority (n = 5) had emitted their first words between 2 and a half and 4 years old. The children in the control group (n = 18) uttered their first word at around 1 year old.

The interviewees reported that most participants in the case group did not speak telegraphic sentences, nor had they developed enough vocabulary to make oral language feasible. Thus, the "not emitted" option was the most selected. On the other hand, most of the control group (n = 19) issued sentences at the appropriate time and currently had an extensive vocabulary, with more than 200 words.

Table 6 shows the medians related to birth condition and lexicon and the statistical comparison between the case and control groups.

Table 5. Characterization of the period of oral language acquisition of children in the case and control groups and comparison between groups

Variables		CASE		CONTROL		p-value
		n	%	n	%	
Emission of the 1st word	1 year	0	0.0%	18	100.0%	< 0.001
	1 and a half years	0	0.0%	2	100.0%	
	2 and a half years	2	100.0%	0	0.0%	
	3 years	0	0.0%	0	0.0%	
	3 and a half years	2	100.0%	0	0.0%	
	4 years	0	0.0%	0	0.0%	
	4 and a half years	1	100.0%	0	0.0%	
	NE	15	100.0%	0	0.0%	
Emission telegraphic sentences	2 years	0	0.0%	19	100.0%	< 0.001
	2 and a half years	0	0.0%	1	100.0%	
	3 years	0	0.0%	0	0.0%	
	3 and a half years	1	100.0%	0	0.0%	
	4 years	1	100.0%	0	0.0%	
	4 and a half years	0	0.0%	0	0.0%	
	5 years	0	0.0%	0	0.0%	
	NE	18	100.0%	0	0.0%	
Words	Fewer than 10	0	0.0%	0	0.0%	< 0.001
	20	2	100.0%	0	0.0%	
	50	2	100.0%	0	0.0%	
	200 or more	0	0.0%	20	100.0%	
	NE	16	100.0%	0	0.0%	

Source: The authors, 2021.
Captions: NE = Words and telegraphic sentences not emitted; n = absolute frequency; % = percentage frequency.
Pearson's chi-square test; significance at $p < 0.05$.

Table 6. Comparison of the medians of variables related to the birth conditions and lexicon of children with and without congenital Zika virus syndrome

Variables	Comparisons				p-value
	CASE		CONTROL		
	Median	IQR	Median	IQR	
1-minute Apgar	9.50	2.00	10.00	0.00	0.728
5-minute Apgar	10.00	2.00	10.00	0.00	0.7563
Age at assessment	3.50	3.00	3.50	3.00	1
Words	0.00	0.00	20.00	0.00	0.001*

Caption: IQR = interquartile range
Source: The authors, 2021. Mann-Whitney test; significance: $p < 0.05$*

DISCUSSION

This study characterized the sample of the control and case groups and the variables related to pregnancy and birth. According to statistical data, most of the data were homogeneous between the groups. However, there was a significant difference in birth weight, use of controlled medications, and speech-language-hearing follow-up.

The newborn's birth weight, gestational age, and general health status are relevant data regarding the time of birth and essential to their prognosis. A retrospective case-control study[9] with 43 newborns with microcephaly due to ZIKV reported no difference between the case and control groups regarding gestational age at birth (both with an average compatible with the full-term classification) and absence of complications at birth (which presupposes that both groups studied were born in good health). The cited study also verified low birth weight in the case group, corroborating the present article's data.

It was found that children with CZS cried excessively and had seizures in early childhood, unlike the comparison group. Excessive crying can be explained by neurological impairments that make it difficult to regulate behavioral states, thus limiting the child's exploration of sensory and motor stimuli, essential to child development. This type of crying (also known as neurological crying) and irritability are the most serious consequences of the epidemic and occur due to the action of the virus during neurological formation, destroying neurons and their abilities, and compromising healthy development[10].

The seizures experienced by those with ZIKV justify the use of controlled medications, of which the most cited by the children's parents/guardians were Keppra, Topiramate, and Depakene. A prospective cohort study[9] interviewed 54 mothers of children with CZS and reported that 30 children developed epilepsy during follow-up up to 2 years old – which was the most frequent complication. It is important to note that untreated seizures can lead to death, cerebral palsy, and neurological damage[11], thus compromising the children's motor, social, cognitive, and linguistic development. Unlike this group, the control group did not have early childhood difficulties, which may imply typical neurological development.

Moreover, in the process of characterizing child development, caregivers reported motor difficulties in the group affected by CZS. Such data agree with the results of an observational cross-sectional study that evaluated the areas of development and the muscle tone of the upper and lower limbs and showed that children affected by microcephaly due to ZIKV had severely impaired motor status, with significant delay in neuropsychomotor development[12].

Most of the case group underwent audiological assessment, and the caregivers reported that the examinations had normal results, except for two children. It is important to highlight that these children also underwent infant hearing screening tests at birth and had normal test results, except for one newborn. Two of these children were diagnosed with hearing loss, according to reports from caregivers, and one used a hearing aid. The control group only underwent infant hearing screening tests at birth, as it is required by the Brazilian Federal Law for all newborns. However, they did not need audiological assessments during child development.

The literature presents little evidence on the involvement of the auditory pathways in ZIKV infection. The data available to date do not provide knowledge of the entire spectrum of involvement of the auditory organs by this virus, do not confirm the causal association between this involvement and infection, and do not rule out progressive hearing loss, especially regarding individuals with central nervous system malformations[13]. Thus, the study population needs auditory monitoring to provide early diagnosis and intervention.

The caregivers reported that the children with CZS mainly communicated through elementary skills, such as shouting, eye contact, and vowels; the first two were the most prevalent. The language development milestones indicate that eye contact is an intentional communicative act when addressing another person and awaiting a response. This is an important milestone that precedes the utterance of the first words[8]. The control group communicated through elaborate linguistic constructions, such as sentences and narratives.

Other language skills were also mentioned by the children's caregivers. A small percentage of children in the case group communicated through dialogue, understood simple orders, performed imitative behaviors, symbolic play, and shared attention – differently from the control group, in which most of the sample performed or had performed these skills.

Having dialogues and understanding simple orders involve the integration of linguistic aspects (e.g., communicative intention, interaction with the

interlocutor, expressive and receptive language, phonetics/phonology, semantics, syntax, pragmatics, and lexicon) and cognitive aspects that enable attention, concentration, perception, and memory. Hence, various domains – besides neurological integrity – must be activated to successfully perform the communicative functions of dialogue and understanding. This justifies the group of children with CZS not achieving these skills as a communicative resource.

Imitative behaviors are part of language, social, and speech development. Children interact in the social context by reproducing models already observed, emitting new sounds by imitating them, and developing language by exploring the world, socializing, and reproducing speech and gestures. The literature states that the ability to imitate contributes to the production and variance of expressive and receptive vocabulary in the first years of life[14]. Such skill requires an organized motor domain, involving global, oral, and manual skills, which the study population (case group) did not have, contributing to their low performance of this skill.

Concomitantly, other skills emerge from those already acquired, thus constituting the child's communicative and cognitive scenario. Shared attention is initially indicated through gestures such as pointing, showing, and giving objects, alternating the gaze between these and the interlocutor's face, and at whose core is the child's intentionality[15]. It is essential to construct social cognition and develop in the sociocultural context – in which shared attention and activities are essential. Thus, it precedes the first manifestations of intentional communication and language ability[16]. Symbolism emerges parallel to the acquisition of language, representing absent fictitious objects, which appears around the age of 2 years[17]. It is important to point out that most caregivers of children with CZS reported the absence of such acquisitions.

Regarding the period of oral language acquisition, a minority of children affected by CZS communicated through simple words and telegraphic sentences. Such acquisitions took place around 2 and a half to 4 years, deviating from the expected chronological period.

According to the literature, children emit their first words at around 10 to 15 months, reaching a vocabulary of 50 words at around 18 months, and morphosyntactic development with telegraphic sentences at around 24 months[18]. Data from the cited research showed that children in the control group emitted and constructed their first elementary sentences as expected for their chronological age.

The medians of variables related to birth conditions and lexicon in children from both groups were homogeneous regarding their 1st and 5th-minute Apgar score and age at assessment. However, a statistical difference was found in the lexicon between the groups. This relationship was already expected, since the main characteristic of children with CZS (case group) is microcephaly – i.e., reduced head circumference. The mean head circumference in this research was 29.8 centimeters (cm), which characterizes microcephaly. Data from the World Health Organization indicate that newborns with a gestational age of 37 weeks or more with a mean head circumference of less than or equal to 31.5 cm (girls) and 31.9 cm (boys) can be diagnosed with microcephaly[19].

Further studies are needed in linguistics and alternative and augmentative communication related to the neurological profile of children with CZS, as this article's characterization showed language skills compatible with the initial acquisition period, compromising their communication and socialization.

The limitations of the study include the sample size and the number of meetings with parents (only one), as data were collected during the pandemic.

CONCLUSION

This case-control study showed statistically homogeneous pregnancy and birth variables between the two groups, which differed only in weight, medication use, and speech-language-hearing follow-up. Early childhood difficulties were evident in the case group, regarding intense crying and seizures.

In the opinion of caregivers, most of the case group communicated non-verbally, through babbling, shouting, and eye contact, whereas the minority communicated through dialogue, understanding simple orders, imitative behaviors, symbolic play, and shared attention. On the other hand, the control group communicated through complex sentences, constructed into narratives.

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ICD, MRDR: Investigation; Supervision.

LNAA: Data curation; Formal analysis.

SMMSA: Methodology; Supervision.

GASA: Methodology; Validation; Supervision.