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Original articles

Evaluation of the maturational auditory process in children with the infection by Zika congenital syndrome

Priscila de A Lucas[1]
Walkiria B Santos[2]
Thalita M de Oliveira[1]
Marcial F Galera[1]

[1] Universidade Federal do Mato Grosso - UFMT, Hospital Universitário Júlio Müller, Cuiabá, Mato Grosso, Brasil.

[2] Centro Universitário de Várzea Grande, Várzea Grande, Mato Grosso, Brasil.

ABSTRACT

Purpose: to analyze the absolute latencies of waves I. III and V and the interpeak intervals I-III. III-V and I-V of the ABR recorded from different age groups of children with congenital zika virus infection and their peers without risk indicators for hearing impairment.

Methods: 84 newborns and infants (N=51 study group and N=33 control group) divided into groups with different post-conceptual ages. with the results of their hearing exams analyzed by age group and compared with their peers without other risk indicators for hearing impairment. The assessment of the auditory pathway was conducted through tympanometry. otoacoustic emissions and auditory brain stem responses.

Results: only the latency of wave I and the interpeak III-V showed no significant difference between the study and control groups. The absolute latency and interpeak values found in the study group were significantly lower than those found in the control group.

Conclusion: the maturation of the brain stem in children with ZIKV infection occurred within normal limits. with no retrocochlear disorders until the age of 5 years.

Keywords: Zika Virus; Evoked Potentials, Auditory, Brain Stem; Hearing; Arbovirus Infections

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Corresponding author:
Priscila de Araújo Lucas
Avenida Bosque da Saúde 841/123 - Bosque da Saúde
Zipcode: 78050-070 - Cuiabá, Mato Grosso, Brazil
E-mail: prilucas@hotmail.com

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INTRODUCTION

Children at risk of hearing impairment and their families must have access to the diagnostic and rehabilitation resources needed to develop their maximum potential in terms of linguistic and social development. Regarding the treatment of children with hearing impairment. it is clear that there is a critical period for the language acquisition and development. once clinical findings demonstrate that children with such impairment. who receive early and appropriate intervention. show auditory and language performance superior to those who begin the process at more advanced ages[1]. Therefore. improving data regarding the diagnosis and maturation of the auditory pathway in specific risk groups for hearing impairment. such as those with Congenital Zika Virus Syndrome (CZVS). is needed to contribute to the early diagnosis of deafness. ensuring intervention in the period of greater neuronal plasticity. in which new neural connections are easily established.

The Joint Committee on Infant Hearing[2] recommends the use of electrophysiological methods in the newborn hearing screening programs such as Auditory Brainstem Responses – (ABR) and Otoacoustic Emissions (OAE). ABR is a simple. objective and non-invasive method used to assess the nerve and the auditory pathways of the brainstem.

ABR is defined as a set of electrical responses generated in various anatomical sites through an external auditory stimulus (auditory or electrical stimulation). This acoustic stimulation generates responses through the sequential and synchronized activation of the nerve fibers along the auditory pathway[2]. ABR is widely used to assess the maturation of the auditory pathway and the recording of these potentials in association with the otoacoustic emissions will contribute to the topographic diagnosis of a series of auditory disorders[3].

The waves that belong to this potential have a time of appearance from the beginning of the stimulation. known as absolute latency. The time difference between the appearance of each wave is known as interval or latency interpeak. Thus. the interpretation of the ABR is made through the analysis of the absolute latencies. interpeak intervals. morphology and amplitude of the waves generated and the reproducibility of the tracing[3,4].

According to the literature. ABRs in neonates and infants are influenced by the maturation process of the auditory system[5] and. the maturation effect is even more evident in the case of premature neonates. thus. the response pattern of these children is different from those born at term[5,6]. The maturation level reveals the speed of conduction and effectiveness of the synapses along the auditory nerve to the brainstem in neonates[7]. The literature also establishes that the maturation process of the auditory pathway occurs in the caudal-rostral order. that is. the more rostral the structure. the longer it takes to reach full maturation[8]. The literature establishes that. as the auditory pathways mature. there is also a shortening of the absolute latencies of waves and interpeak intervals and the wave V latency is the last to decrease[5]. The studies mentioned reinforce that the brainstem undergoes the maturation process up to 18 months of age.

The Protocol for Health Care and Response to the Occurrence of Microcephaly Related to Zika Virus (ZIKV) Infection[9]. recommends the presence of the microcephaly as a risk indicator for hearing impairment (RIHI). In children with RIHI. the Newborn Hearing Screening (NHS) is carried out using ABRs due to the higher prevalence of retrocochlear hearing loss. which is not identified by the otoacoustic emissions test[10]. Retrocochlear hearing loss is characterized by disorders of the auditory nerve that alter the information correctly processed by the inner ear when transmitted in the form of electrical impulses to the brain[11]. An integrative review[12] on auditory findings in patients infected with ZIKV concluded that evidence on the involvement of the auditory pathways in congenital or acquired ZIKV infection is still scarce. The data available so far do not allow knowledge of the whole spectrum of involvement of the auditory organs by ZIKV infection or confirm the causal association between this involvement and infection by the virus. They also do not rule out progressive hearing impairment.

Studies already conducted about the power of ZIKV toxicity showed that the virus acts by killing the cells that give rise to neurons. thus impairing the neural communication and causing a diminished cortex and even hypoplasia at the level of the brainstem[13]. A study concluded that the auditory impairment in microcephaly is a common neurodeficit that can be authentically assessed through ABR and that auditory impairment in microcephalic individuals is due to the insufficiency of the central components in the auditory pathway at the level of the brainstem[14]. In view of the above. the question arises: Does the maturation of the auditory pathways of the children with ZIKV congenital syndrome occur similarly to their peers without RIHI?

Due to the importance of evaluation methods in the diagnosis of auditory disorders in children. and the increased demand from newborns and infants with syndrome of the ZIKV congenital infection for early identification of auditory disorders. it is essential to obtain normative data in different age groups. Such data allow knowing response patterns in this population and differentiating them from real alterations. contributing to interpret the results and increasing the accuracy of the audiological diagnosis. Moreover. previous studies highlight the need to assess the population infected by ZIKV infection at an older age.

This study aimed to analyze the absolute latencies of waves I. III and V and the interpeak intervals I-III. III-V and I-V of the ABR recorded in different age groups (newborns - 3 months; 4-9 months and 4 -5 years) of children presented with Zika virus congenital infection and their peers with no risk indicators for hearing impairment (RIHI).

METHODS

This research was approved by the Research Ethics Committee of the Júlio Müller University Hospital (JMUH), Brazil, under number 4.815.346 and CAAE number 46830621.0.0000.5541. All guardians signed the Informed Consent Form (ICF).

This was a case-control study carried out through the analysis of the traces of electrophysiological tests (ABR-click) recorded in newborns and children who were treated at the audiology clinic in the Hospital Universitário Júlio Muller (HUJM) the city of Cuiabá-MT. Children whose guardians sought treatment at HUJM and who had diagnosis of vertical infection by ZIKV were referred for audiological assessment.

This diagnosis was made by detectable Reverse Transcription Polymerase Chain Reaction (RT-PCR) or immunoglobulin M (IgM) reactive for ZIKV in the pregnant mother of the children born with microcephaly and also by the presence of IgM reactive for ZIKV in the child or clinical epidemiological criteria and neuroimaging tests for ZIKV (excluding other congenital infections such as toxoplasmosis. cytomegalovirus. rubella. herpes simplex virus infection. human immunodeficiency virus (HIV). syphilis and parvovirus). The children also had measured the immunoglobulin G (IgG) for ZIKV using the enzyme immunoassay (ELISA) technique and those who maintained reactive IgG even after 18 months of life were considered vertically infected. excluding the possibility of the presence of passive maternal antibodies after this age. Due to the concomitant circulation of distinct arboviruses in the virological panorama of the Americas and the extensive cross-reactivity with other flaviviruses. serologies for the dengue (DENV) and chikungunya (CHIKV) viruses were also performed. ruling out such infections.

Children from 0 months to 5 years of age. vertically infected by ZIKV and their peers without any risk indicator for hearing impairment who had results within normal limits in the proposed hearing assessments were included. Exclusion criteria were: ABR with alterations caused by conductive impairment. cochlear or retrocochlear hearing loss and. middle ear alterations indicated by tympanometry. Furthermore. patients with congenital infections such as. herpes. cytomegalovirus. toxoplasmosis. rubella. syphilis and HIV were excluded from the study. Staying in the intensive care unit ICU for more than five days. parental consanguinity and family history of congenital deafness were also exclusion criteria.

The final sample was composed of 84 patients. divided into groups based on the age group. as follows:

Study group:

- Age group 1 (0-3 months): 22 full term born infants with ZIKV congenital infection. a gestational age greater than 37 weeks. assessed between 37 and 40 weeks;
- Age group 2 (4-9 months): 16 full term born babies with ZIKV congenital infection. assessed at 6 months of age;
- Age group 3 (4-5 years): 13 full term born children. with ZIKV congenital infection. assessed at 5 years of age.

Control group:

- Age group 1 (0-3 months): 11 full term infants. without RIHI. a gestational age greater than 37 weeks. assessed between 37 and 40 weeks;
- Age group 2 (4-9 months): 16 full term babies born. without RIHI. assessed at 6 months of age;
- Age group 3 (4-5 years): six full term children. without RIHI. assessed at 5 years of age.

For inclusion in the study. the procedures described below were carried out. Analysis of the middle ear through tympanometry. using the AT235 equipment from the Interacoustics® brand. The normality criterion adopted was compliance between 0.3 and 1.4 ml obtained at pressures between -100 and +100 daPa[15].

Then. transient stimulus-evoked otoacoustic emissions (TEOAE) were recorded using

Interacoustics® Otoread equipment. The normality criterion adopted was the presence of a response in the 2. 3 and 4 KHz frequency bands with a signal-to-noise ratio greater than 6 dB up to 3 months of age and above 3 dB from that age onwards[16].

The neurodiagnosis was conducted by analyzing the Auditory Brainstem Response (ABR) with click stimulus. using equipment model EB9400 from the Nihon Kohden® brand. A click stimulus with rarefied polarity was used. with a presentation speed of 27.1 clicks/second and a recording window of 12 ms. A total of 1.024 to 2.048 clicks were presented twice for the analysis of the generated tracing. thus reproducibility between tracings could be observed. A DR531 supra-aural headphone Elega® brand was used. and responses were captured using surface electrodes. fixed with adhesive tape and positioned based on to the international 10-20 system (Cz - forehead and M2 and M1 - right and left mastoids). with impedance adjustment below 5 kΩ. The subjects' skin was cleaned with abrasive paste and. for better electrode contact. electrolytic paste was applied to the electrodes. The normality standard adopted for the equipment used was obtained by a national study[17].

The ABR variables analyzed were the absolute latencies of the waves I. III and V and the interpeak intervals I-III. III-V and I-V at the moment of the investigation of the integrity of auditory pathways in the brainstem at an intensity of 80 dBHL in each ear separately.

The audiological assessments mentioned above were conducted in a silent. electrically protected room. by an audiologist expert in the click-ABR analysis and all exams were performed with the child in natural sleep.

For the statistical analysis of data. a significance level of 0.05 (5%) was used. Parametric statistical tests were applied. as the normality of the quantitative variables of main outcome was tested using the Kolmogorov-Smirnov test ($N \geq 30$) and concluded that there is normal distribution.

Initially. it was checked whether there was a statistical difference between the ears in the analysis of absolute latencies and interpeaks recorded in the ABR of the total participants ($N=84$). Then. the analysis was carried out regardless of the group or age group. using the Paired T-Student test (when the same individual is research and control). Next. the performance of the analyzed variables between the groups (Study and Control) was compared using the T-Student test. A final analysis was carried out on six children who attended the sequential assessments. making it possible to carry out a longitudinal analysis. To this end. the Repeated Measures ANOVA test was applied to verify the evolution of results between age groups and the Tukey Multiple Comparison test (post-hoc) to determine precisely between which moments there was a difference in the values of the variables analyzed.

RESULTS

There is no mean difference statistically significant between the ears neither for latencies nor for interpeaks in Table 1. Therefore. the next analyzes considered both ears. aiming to have a larger sample. which will demonstrate greater reliability of the results.

Table 1. Comparison of the ears regarding latencies and interpeaks

Absolute latencies and interpeak intervals		Mean	Median	Standard deviation	CV	Min	Max	N	CI	P-value
Latency I	RE	1.58	1.56	0.15	9%	1.33	2.12	84	0.03	0.361
	LE	1.59	1.61	0.12	8%	1.33	1.88	84	0.03	
Latency III	RE	4.05	4.05	0.40	10%	3.15	5.00	84	0.08	0.448
	LE	4.04	4.01	0.37	9%	3.33	4.85	84	0.08	
Latency V	RE	6.17	6.26	0.53	9%	5.15	7.18	84	0.11	0.370
	LE	6.16	6.17	0.51	8%	5.15	7.09	84	0.11	
Interpeak I-III	RE	2.46	2.49	0.34	14%	1.73	3.33	84	0.07	0.356
	LE	2.44	2.46	0.35	14%	1.66	3.28	84	0.07	
Interpeak III-V	RE	2.12	2.10	0.26	12%	1.67	2.83	84	0.06	0.869
	LE	2.13	2.12	0.28	13%	1.38	3.11	84	0.06	
Interpeak I-V	RE	4.58	4.60	0.48	11%	3.56	5.42	84	0.10	0.123
	LE	4.55	4.59	0.48	11%	3.42	5.52	84	0.10	

Captions: RE: right ear; LE: left ear; CV: Coefficient of Variation; Min: Minimum; Max: Maximum; CI: Confidence Interval; N=84. Paired t-Test.

There was no mean difference statistically significant between the groups only for latency I and interpeak III-V in Table 2. Statistical significance was obtained in at least one age group regarding the other latencies or interpeaks. It is also observed that the mean values of latencies and interpeaks found in the study groups were lower in relation to the control group.

Table 2. Comparison of the groups by age group in relation to latencies and interpeaks

Absolute latencies and interpeak intervals			Mean	Median	Standard deviation	CV	Min	Max	N	CI	P-value
Latency I	Range 1	Control	1.61	1.59	0.13	8%	1.42	1.82	22	0.05	0.347
		Study	1.64	1.62	0.13	8%	1.33	1.88	44	0.04	
	Range 2	Control	1.58	1.54	0.15	10%	1.36	2.12	32	0.05	0.899
		Study	1.59	1.58	0.09	6%	1.44	1.85	32	0.03	
	Range 3	Control	1.50	1.50	0.11	7%	1.37	1.67	12	0.06	0.520
		Study	1.53	1.53	0.14	9%	1.33	1.84	26	0.05	
	General	Control	1.58	1.55	0.14	9%	1.36	2.12	66	0.03	0.358
		Study	1.60	1.59	0.13	8%	1.33	1.88	102	0.03	
Latency III	Range 1	Control	4.32	4.27	0.25	6%	3.97	4.74	22	0.10	0.703
		Study	4.29	4.21	0.35	8%	3.50	5.00	44	0.10	
	Range 2	Control	4.19	4.20	0.23	6%	3.82	4.64	32	0.08	<0.001*
		Study	3.89	3.91	0.24	6%	3.48	4.41	32	0.08	
	Range 3	Control	3.76	3.77	0.17	5%	3.48	3.98	12	0.10	0.001*
		Study	3.53	3.53	0.19	5%	3.15	3.92	26	0.07	
	General	Control	4.16	4.19	0.30	7%	3.48	4.74	66	0.07	0.002*
		Study	3.97	3.95	0.42	10%	3.15	5.00	102	0.08	
Latency V	Range 1	Control	6.58	6.65	0.35	5%	5.75	7.18	22	0.15	0.559
		Study	6.53	6.62	0.38	6%	5.70	7.06	44	0.11	
	Range 2	Control	6.36	6.45	0.31	5%	5.79	6.84	32	0.11	<0.001*
		Study	5.96	5.97	0.26	4%	5.45	6.54	32	0.09	
	Range 3	Control	5.64	5.61	0.22	4%	5.31	5.94	12	0.13	0.009*
		Study	5.45	5.44	0.20	4%	5.15	5.97	26	0.08	
	General	Control	6.31	6.41	0.45	7%	5.31	7.18	66	0.11	0.004*
		Study	6.07	6.06	0.54	9%	5.15	7.06	102	0.10	
Interpeak I-III	Range 1	Control	2.71	2.64	0.23	8%	2.43	3.14	22	0.09	0.290
		Study	2.64	2.56	0.30	11%	2.03	3.33	44	0.09	
	Range 2	Control	2.61	2.55	0.21	8%	2.27	3.15	32	0.07	<0.001*
		Study	2.31	2.31	0.22	9%	1.90	2.74	32	0.08	
	Range 3	Control	2.26	2.27	0.16	7%	2.08	2.53	12	0.09	<0.001*
		Study	1.99	2.02	0.19	9%	1.66	2.37	26	0.07	
	General	Control	2.58	2.54	0.26	10%	2.08	3.15	66	0.06	<0.001*
		Study	2.37	2.36	0.36	15%	1.66	3.33	102	0.07	
Interpeak III-V	Range 1	Control	2.26	2.28	0.25	11%	1.78	2.70	22	0.11	0.975
		Study	2.26	2.21	0.28	12%	1.80	3.11	44	0.08	
	Range 2	Control	2.17	2.15	0.26	12%	1.38	2.57	32	0.09	0.054
		Study	2.07	2.03	0.14	7%	1.76	2.34	32	0.05	
	Range 3	Control	1.88	1.88	0.16	9%	1.69	2.19	12	0.09	0.720
		Study	1.91	1.91	0.20	11%	1.45	2.24	26	0.08	
	General	Control	2.15	2.14	0.27	13%	1.38	2.70	66	0.07	0.391
		Study	2.11	2.10	0.27	13%	1.45	3.11	102	0.05	
Interpeak I-V	Range 1	Control	4.98	4.98	0.34	7%	4.21	5.49	22	0.14	0.223
		Study	4.86	4.97	0.35	7%	4.10	5.52	44	0.10	
	Range 2	Control	4.78	4.75	0.31	6%	4.22	5.36	32	0.11	<0.001*
		Study	4.37	4.43	0.25	6%	3.84	4.81	32	0.09	
	Range 3	Control	4.14	4.14	0.20	5%	3.84	4.49	12	0.11	0.002*
		Study	3.90	3.85	0.22	6%	3.42	4.39	26	0.08	
	General	Control	4.73	4.77	0.42	9%	3.84	5.49	66	0.10	<0.001*
		Study	4.46	4.44	0.49	11%	3.42	5.52	102	0.10	

Captions: CV = Coefficient of Variation; Min = Minimum; Max = Maximum; CI = Confidence Interval; N(control) = 66; N (study) = 102; t-student test;
*: significance <0.05

Table 3 shows that there is mean difference statistically significant between age groups for almost all analyses. with the exception of latency I.

Table 3. Comparison of age groups in the study group in relation to latency and interpeak

Absolute latencies and interpeak intervals		Mean	Median	Standard deviation	CV	Min	Max	N	CI	P-value
Latency I	Range 1	1.59	1.54	0.12	8%	1.50	1.88	12	0.07	0.849
	Range 2	1.57	1.54	0.08	5%	1.48	1.70	12	0.05	
	Range 3	1.59	1.61	0.14	9%	1.40	1.84	12	0.08	
Latency III	Range 1	4.06	4.11	0.24	6%	3.50	4.33	12	0.13	<0.001*
	Range 2	3.69	3.63	0.16	4%	3.48	3.97	12	0.09	
	Range 3	3.51	3.48	0.21	6%	3.18	3.92	12	0.12	
Latency V	Range 1	6.32	6.35	0.47	8%	5.70	7.03	12	0.27	<0.001*
	Range 2	5.75	5.76	0.22	4%	5.45	5.97	12	0.13	
	Range 3	5.37	5.41	0.14	3%	5.15	5.60	12	0.08	
Interpeak I-III	Range 1	2.47	2.55	0.17	7%	2.03	2.61	12	0.10	<0.001*
	Range 2	2.12	2.11	0.16	7%	1.90	2.43	12	0.09	
	Range 3	1.91	1.88	0.15	8%	1.66	2.19	12	0.09	
Interpeak III-V	Range 1	2.22	2.22	0.34	15%	1.80	2.82	12	0.19	0.027*
	Range 2	2.06	2.00	0.14	7%	1.91	2.34	12	0.08	
	Range 3	1.84	1.90	0.21	11%	1.45	2.18	12	0.12	
Interpeak I-V	Range 1	4.69	4.73	0.45	10%	4.10	5.42	12	0.26	<0.001*
	Range 2	4.18	4.18	0.23	5%	3.84	4.49	12	0.13	
	Range 3	3.75	3.80	0.16	4%	3.42	4.00	12	0.09	

Captions: CV = Coefficient of Variation; Min = Minimum; Max = Maximum; CI = Confidence Interval; N = 12; *: significance value <0.05. repeated measures ANOVA test.

Table 4 only shows the p-values for comparisons between age groups. In this table. cross the line with the column to find the required p-value. Thus. analyzing this table of p-values. there is a statistically significant difference between all age groups. with the exception of the III-V interpeak. where there is no difference in Range 1 - mean of 2.22 compared to the Range 2 - mean 2.06 (p = 0.150).

Table 4. P-values from the post-hoc comparison regarding Table 3

Absolute latencies and interpeak intervals		Range 1	Range 2
Latency III	Range 2	<0.001*	
	Range 3	<0.001*	0.021*
Latency V	Range 2	0.002*	
	Range 3	<0.001*	<0.001*
Interpeak I-III	Range 2	<0.001*	
	Range 3	<0.001*	0.006*
Interpeak III-V	Range 2	0.150	
	Range 3	0.009*	0.022*
Interpeak I-V	Range 2	0.002*	
	Range 3	<0.001*	<0.001*

*significance value <0.05. Tukey Multiple Comparison Test.

DISCUSSION

The development of the complete auditory pathway. including peripheral and central parts. has a fundamental role in the language development and impacts academic and social skills in an individual's life. The peripheral auditory pathway transmits the electrical sound impulse to the central auditory pathways. The electrically coded messages run through the auditory nerve until reach the brainstem. and from this point. to the right and left cerebral hemispheres. where they are processed and interpreted [18].

Regarding the evaluation of peripheral structures in the auditory system in children infected by ZIKV. it is known that there is cochlear involvement. with a variable incidence between studies[12.19.20]. The relationship between hearing loss and the presence of microcephaly is also controversial[21-24]. Regarding the pathophysiology of the virus. a study shows that it lodges in cochlear regions. but it is not known whether the damage is caused by the direct virus action or by the host's immune reaction[25].

The ZIKV infection is considered a risk factor for hearing impairment due to its neurotropic characteristic. The Zika virus epidemic on Brazil 2015 caused a large number of cases of microcephaly in the children of infected pregnant women and. the Ministry of Health (MS) launched several strategies to finish the situation. among them the document entitled "Protocol for attention and response to the occurrence of microcephaly related to Zika virus infection". which was published in 2015 and 2016[9]. The protocols recommend that children with RIHI should be assessed preferably using ABR due to the higher prevalence of retrocochlear hearing loss that cannot be identified through the OAE test.

Analyzing the sound transmission through the brainstem in children with ZIKV and their peers without RIHI. it was demonstrated through this study that there was a statistical difference between the groups assessed in the values of absolute latency (waves III and V) and interpeak (I-III and I-V) for all age groups. except age group 1.

The descriptive analysis showed a lower average latency in the group of children with ZIKV. a finding corroborated by a national study[26]. This finding may be justified by the smaller size of the central structures of children with ZIKV. such as brainstem hypoplasia[27.28]. not being attributed to a maturational factor.

Brainstem abnormalities are findings described from 21% to 70% of the patients with ZIKV congenital infection. being characterized by a thinned brainstem. with an atrophic appearance. which may be related to the synergism of the reduction in the number of descending fibers and direct viral action[29].

According to the literature. the wave I is generated in the distal portion of the cochlear nerve. informs the peripheral conduction velocity and is practically mature at birth[27]. This indicates that the maturation of the auditory pathways involves different mechanisms in central and peripheral areas. once the stimulus conduction depends on changes in velocity associated with myelination and changes in synaptic efficiency of various nuclei of the auditory pathway[31]. Thus. the stability between groups in relation to wave I latency found in the present study is justified by this fact and confirms results from previous studies[29-33].

The electrical response of the brainstem to a sound stimulus is complex and uses several redundancies throughout its nuclei. Thus. the interpeak intervals demonstrate not only the transmission speed of the impulse. but also the synchrony between them. The interpeak interval III-V reflects the neural synchrony exclusively within the brainstem[34] with no difference between the groups regarding this aspect in the present study. The findings reflect that there are no changes in neuroconduction in the brainstem for the population infected by ZIKV. which corroborates a national study[35]

In this study. an analysis of the longitudinal monitoring of six children (12 ears) was carried out. The absolute latencies (III and V) and interpeaks (I-III. III-V and I-V) showed decreased latencies throughout the monitoring with a significant difference. There was no difference in latency of the wave I during auditory monitoring. which is justified by the fact that it reflects activation of the distal part of the auditory nerve and it is mature at birth[30].

The wave III is formed in the region of the superior olivary complex (pons) and the wave V. at the level of the lateral lemniscus (low midbrain). The literature clearly establishes that the maturation process of the auditory pathway occurs in the caudal-rostral order. thus the more rostral the structure. the longer it takes to reach full maturation[31.32.36]. The development process of the auditory system occurs by the increment of neuronal myelination and greater synchronization of electrical conduction. which. in the prenatal phase is directed by biological factors intrinsic to the individual. At this stage. the development can be altered by genetic factors or disorders in metabolic control. In the perinatal and postnatal phases. a priori. it is sensory

privation that exerts a negative impact on auditory development[37].

Thus. it can be interpreted that the difference observed in latency of the waves III and V may be explained by the occurrence of auditory maturation between the tests in most babies. Regarding the analysis of the interpeak intervals I-III. III-V and I-V. it may be confirmed the occurrence of auditory maturation between the initial and subsequent exams. This data converges with the literature. which establishes that with the maturation of the auditory pathways. there is also a shortening of the absolute latencies of waves and interpeak intervals. with the latency of wave V being the last to decrease[31.32]. The findings demonstrate that the maturation of the auditory pathway in children infected by ZIKV occurs in a similarly to the control group.

It is emphasized that all children assessed in the sample showed OAE present for both ears with ABR results within normal limits at all assessment times. Therefore. there was no presence of progressive hearing loss in the sample members up to five years of age. A national study[37] assessed 107 children up to three years of age with ZIKV infection and also found no progressive hearing loss in the sample.

The exact location of the auditory lesion caused by ZIKV is still uncertain[12]. Audiological tests have shown cochlear disorders. brainstem synchrony within the normal range and alterations in tests that assess essential cortical functions for language development[37-39]. A study that assessed 88 children infected by ZIKV with normal hearing thresholds found delayed development of communication skills in 87.5% of the sample. especially in those with greater neurological impairment[40]. Therefore. there is a need for auditory monitoring of children with Zika Virus Congenital Syndrome (ZCS) at birth and at 12 months. due to the importance of stimulating auditory and communication skills for a better language development and learning. based on the documents issued by competent organizations[10]. Moreover. the importance of referral for early stimulation in a rehabilitation service is highlighted[9].

In the comparison of absolute latencies and interpeak intervals carried out between the study age groups (0-3 months. 4-9 months. 4-5 years) a statistical difference was demonstrated. which once again reinforces the need to observe auditory maturation in a every six months by reducing latencies. as recommended by national and international bodies[1.9.10]. This study was carried out during the COVID19 pandemic. which made it difficult for patients to travel to the hearing assessment center. even after authorization by local authorities. Furthermore. there was difficulty in contacting some patients through initial registration. and they could not be scheduled to carry out sequential assessments. These factors reduced the number of individuals evaluated.

Children with ZCS show lower performance in the pragmatic aspects of language. less use of communicative functions (informative and narrative). lower level of verbal communication means. contextualization. verbal comprehension and expressive vocabulary when compared to children in the comparative group[40]. Future studies that include behavioral evaluation of the auditory processing. as well as electrophysiological assessment of middle and long latency auditory pathways in this population will be recommended. Questions as: “How does a child with ZCS and normal hearing thresholds process sounds in the environmental noise?”; “Is there a difference in auditory performance between the ears?”; “Is central auditory behavior influenced by the presence of microcephaly?” will answer in order to guide public policies for reception and intervention in these cases. since the early stimulation teams must offer guidance to parents and the community about the possibilities of monitoring from the neonatal period until the child’s school stage.

CONCLUSION

The absolute latencies of waves III and V. as well as interpeak intervals I-III and I-V. were lower in the study group and statistically different between the groups with and without ZCS. Latencies studied decreased over time for both groups. There was no progressive hearing loss in the group longitudinally followed until the age of five years.

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Author 's contributions:

PAL; MFG: Conceptualization; Funding acquisition; Formal analysis; Writing - original draft.

WBS; TMO: Funding acquisition; Formal analysis; Writing - review & editing.