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Research article

Audiological follow-up of children with congenital Zika syndrome

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ABSTRACT

How does the auditory function of children with congenital Zika syndrome present during the first three years of life? To determine the auditory function of children with congenital Zika syndrome during the first three years of life and estimate the frequency and long-term presentation of hearing loss in this syndrome, an auditory assessment with screening and diagnostic tests was conducted. The screening test consisted of measuring the short latency ABR using click stimuli. If the ABR click indicated hearing loss, confirmation was obtained with a frequency-specific ABR (FS-ABR), in which the stimuli were tone bursts at frequencies of 500 and 2000 Hz by bone and air conduction. This case series included 107 children with confirmed congenital Zika syndrome, and the cumulative incidence of sensorineural hearing loss in the first three years of life was 9.3% (10/107). There were no cases of delayed-onset or progressive deficits in hearing. Early presentation of sensorineural hearing loss seems to occur with a higher frequency in children with congenital Zika syndrome than in the general population. Sensorineural hearing loss resulting from congenital Zika virus infection does not appear to present with delayed onset or with progressive deficits.

1. Introduction

Severe microcephaly with partially collapsed skull, brain abnormalities, including thin cerebral cortices and subcortical calcifications, macular scarring and focal pigmentary retinal mottling, congenital contractures, including arthrogryposis and clubfoot, and hypertonia are the five clinical features that have been proposed to distinguish congenital Zika syndrome (CZS) from other congenital infections [1, 2, 3, 4]. However, the full spectrum of manifestations remains unknown, in part because CZS is a recently described syndrome and the first reported cases were the most severe. Current understanding of the syndrome is further limited by the lack of published longitudinal studies of children with intrauterine exposure to Zika virus [5, 6]. In addition to classical cortical neurological damage, congenital Zika virus infection may also lead to functional disabilities, such as swallowing disorders, visual impairment in the absence of structural ocular abnormalities [7], and hearing loss [4, 8, 9, 10, 11]. While there is strong evidence that children congenitally infected with Zika virus exhibit abnormalities at the time of delivery, several studies have reported late-onset microcephaly among infants born with a normal head circumference, raising the hypothesis that there may be continued viral activity in neural tissue, even after birth [12, 13].

In 2016, our group published the first case report of hearing loss associated with congenital Zika syndrome [8]. In a subsequent investigation of 69 infants with microcephaly caused by confirmed congenital Zika virus infection, we found that hearing loss was prevalent in 5.8% of patients who were evaluated at a mean age of 3.8 months [4]. Considering that other congenital viral infections, such as congenital cytomegalovirus (CMV) infection and congenital rubella syndrome [14, 15, 16], may become symptomatic over time, it would be reasonable to consider whether sensorineural hearing loss (SNHL) due to CZS may also present with the same progressive behavior. Therefore, the aim of

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the current study was to describe the frequency of hearing loss in children with CZS across the first three years of life and to determine if this impairment may present with late onset or progressively over time.

2. Materials and methods

2.1. Design and population

We conducted a prospective observational study from November 2015 to August 2019. The case series included children, ages 0-3 years, with suspected CZS who were referred to the Hospital Agamenon Magalhães, a center for hearing loss and rehabilitation in Recife, Pernambuco, Brazil. Suspected cases of CZS were identified based on the clinical criteria for microcephaly established by the Ministry of Health of Brazil, which, in the early period of the epidemic, was a head circumference smaller than 32 centimeters. However, this study included only children with congenital Zika virus infection confirmed by a positive Zika virus-specific IgM capture enzyme-linked immunosorbent assay performed on cerebrospinal fluid [17], during the neonatal period.

2.2. Data collection

The study was approved by the Hospital Agamenon Magalhães Ethics Committee on Research (Protocol Number 1.472.742). Informed consent of all families of the children participating in this study was obtained prior to the start of the research, and the privacy rights of all the children were ensured.

From 255 children with suspected CZS referred to the Hospital Agamenon Magalhães, 138 tested positive for Zika virus infection. These children were monitored for a period of up to three years with reassessments at variable intervals. From 138 children, 30 were excluded from the study due to missing follow-up, thereby resulting in a total of 108 participants.

Zika virus–associated microcephaly was defined as head circumference of two standard deviations (SDs) below the mean for newborn gestational age and sex, according to the INTERGROWTH-21st charts. Abnormal cranial computed tomography (CT) or magnetic resonance imaging (MRI) findings, such as subcortical calcifications, were considered consistent with CZS [1, 13]. Other infectious causes of congenital SNHL, including CMV, toxoplasmosis, herpes simplex or syphilis, were excluded by serologic testing of infants and their mothers. When cytomegalovirus IgG was present in both the mother and child, further nucleic acid amplification testing for cytomegalovirus DNA was performed using urine or blood samples.

Data were also collected on the presence and timing of rash during pregnancy and on maternal or perinatal risk factors for congenital hearing loss, such as: alcohol consumption, family history of hearing loss, neonatal intensive care of more than five days, very preterm birth (i.e., less than 32 weeks gestational age), ototoxic drug exposure, birth trauma, postnatal infections or other risk factors for hearing loss [18]. Participants with at least one risk factor for early childhood hearing loss were excluded from the current analysis. One child was excluded due to exposure to an ototoxic drug, thereby reducing the study sample to 107 participants.

Auditory assessment was conducted through screening and diagnostic tests, as recommended by the American Academy of Pediatrics and the Joint Committee on Infant Hearing [18]. Initially, an auditory brainstem response (ABR) test was scheduled for all of the children every six months. However, not all of the children were able to attend the examinations regularly and, therefore, it became necessary to modify the follow-up interval to at least annual assessments. The screening test consisted of measuring the short latency auditory brainstem response using click stimuli (Click-ABR). The acquisition parameters for the screening tests were as follows: a filtered click stimulus (33–1500 Hz); a stimulation rate of 27.5 milliseconds; rarefied polarity; ipsilateral register; an analysis time of 25 milliseconds; an intensity of 35 dB nHL; and a minimum number of 2,400 stimuli. The children's skin was prepared using brand-specific, abrasive paste and disposable electrodes placed at the Fz, Fpz and M1/M2 positions. We used disposable insert phones and electrodes. Normal was considered when wave V was identified in two consecutive average waveforms of 35 decibels at a normalized hearing level (nHL). If the first screening test with Click-ABR was normal, follow-up tests were performed with Click-ABR yearly. If the first screening test was abnormal, a second test with Click-ABR was repeated within one month.

If this second test with Click-ABR also indicated hearing loss, then diagnostic confirmation and follow-up of these children were performed with a frequency-specific ABR (FS-ABR), in which the stimuli consisted of tone bursts at frequencies of 500 and 2000 Hz by bone and air conduction. Acquisition parameters by air conduction were as follows: a high-pass filter of 33 Hz and a low-pass filter of 1500 Hz; a stimulation rate of 27.5 milliseconds; rarefied polarity; ipsilateral register; an analysis time of 25 milliseconds; and a minimum number of 2,400 stimuli. When bone conduction was used, the acquisition parameters were as follows: a high-pass filter of 33 Hz and low-pass filter of 1500 Hz; a stimulation rate of 37.7 milliseconds; alternating polarity; ipsilateral register; and analysis time of 25 milliseconds; and a minimum number of 2,400 stimuli. To collect data by bone conduction, a transducer was used.

The initial intensity used to search for the electrophysiological threshold using tone bursts by air conduction was 60 dB nHL and by bone conduction was 40 dB nHL. When wave V was not identified, the stimulus was increased, and if it was identified, it was decreased until it disappeared.

Click stimuli at 80 dB nHL were used to check for the presence of cochlear microphonics when there was no response at tone burst ABR. This search used the same acquisition parameters described above for the short latency auditory brainstem response (ABR) using click stimuli; however, two recordings with the condensed polarity and at least one with tube obstruction of insert earphones were made.

A diagnosis of hearing loss was confirmed, if hearing thresholds obtained by FS-ABR exceeded 35 dB nHL at 500 Hz and 25 dB nHL at 2000 Hz by air conduction. Bone conduction was also assessed to classify the type of hearing loss at the same frequencies, according to data by Elsayed et al. for the 95th percentile [19]. The same protocol was applied for the reassessment at the 1-month follow-up. Conductive hearing loss was not considered to be related to Zika virus infection since this kind of impairment is caused by mechanical problems in the middle or external ear, which is not the case in congenital viral infections. Thus, only SNHL was attributed to the virus.

All of the children were assessed by ABR in the first year of life and at least one more time during annual evaluations over the three years of follow-up. If more than two assessments were performed, then we investigated the first and last assessments for this study.

2.3. Statistical analyses

All analyses were performed using the Statistical Package for the Social Sciences 13.0, by SPSS, Inc., Chicago, Illinois. Absolute and relative frequencies were tabulated and are presented with 95% confidence intervals. Numerical variables are described by measures of central tendency and dispersion; the assumption of normality was investigated using the Kolmogorov–Smirnov test. Associations between categorical variables were evaluated using Fisher's exact test, and associations between continuous variables were evaluated using Student's t-test.

3. Results

The present study followed up 107 children. The mean age of the children was 4.5 months at the first hearing evaluation and 29.3 months at the last exam. The average number of screening tests performed within the population was four. All children had head circumferences

Table 1. Follow-up – Hearing screening (Click-ABR) in the first three years of life in children with congenital Zika syndrome.

RESULT	1st EXAM			LAST EXAM		
	n	%	MA	n	%	MA
Passed in both ears	85/107	79.4	4.9	87/107	81.3	29.2
Failed in one or both ears	22/107	20.6	3.2	20/107	18.7	29.4

Abbreviations: MA = mean ages in months.

Table 2. Characterization of the type of hearing loss found during three years of follow-up of children with congenital Zika syndrome, based on diagnostic FS-ABR.

RESULT	1st EXAM			LAST EXAM		
	n	%	MA	n	%	MA
Normal	4/22	18.2	2.4	0		
Conductive hearing loss	7/22	31.8	4.7	10/20	50.0	28.1
Sensorineural hearing loss	11/22	50.0	5.1	10/20	50.0	27.6

Abbreviations: MA = mean ages in months.

Table 3. Characterization of confirmed sensorineural hearing loss in children with congenital Zika syndrome using frequency-specific auditory brainstem response.

Case No.	Sex	HC cm/SD	Age of first Click-ABR	Age of diagnostic of SNHL	Age of last FS-ABR	FS-ABR*				Hearing Characterization
						RE		LE		
						500 Hz	2000 Hz	500 Hz	2000 Hz	
1	M	28/3	2	3	30	85 dB nHL	80 dB nHL	80 dB nHL	80 dB nHL	Bilateral moderate SNHL
2	M	28/3	5	6	27	65 dB nHL	45 dB nHL	25 dB nHL	25 dB nHL	Unilateral moderate SNHL (RE)
3	M	29/3	7	8	25	70 dB nHL	80 dB nHL	45 dB nHL	40 dB nHL	Bilateral SNHL (Moderate on right/mild on left)
4	M	29/3	3	4	22	NR	NR	NR	NR	Bilateral profound SNHL
5	F	26/3	5	5	32	25 dB nHL	20 dB nHL	40 dB nHL	50 dB nHL	Unilateral mild SNHL (LE)
6	F	25/3	1	2	26	80 dB nHL	65 dB nHL	70 dB nHL	50 dB nHL	Bilateral moderate SNHL
7	M	26/3	5	7	36	NR	NR	25 dB nHL	25 dB nHL	Unilateral profound SNHL (RE)
8	F	28/3	5	6	19	55 dB nHL	65 dB nHL	50 dB nHL	70 dB nHL	Bilateral moderate SNHL
9	M	26/3	8	9	30	30 dB nHL	20 dB nHL	50 dB nHL	55 dB nHL	Unilateral moderate SNHL (LE)
10	M	26/3	1	2	30	100 dB nHL	90 dB nHL	25 dB nHL	20 dB nHL	Unilateral severe SNHL (RE)

Abbreviations: dB = decibels; dB nHL = decibels normalized hearing level; Hz = Hertz; LE = left ear; RE = right ear; FS-ABR = frequency-specific auditory brainstem response; HC = head circumference at birth; SD = standard deviation; SNHL = sensorineural hearing loss; NR = no response;
*Bone conduction thresholds did not characterize conductive hearing loss and were omitted from this table.

below 32 centimeters, and only 13 did not have microcephaly according to the INTERGROWTH-21st charts. While not all of the children underwent neuroimaging assessments, those who were assessed had neuroimaging findings consistent with CZS.

In total, 22 (20.6%) children failed the first screening test with Click-ABR (Table 1). These 22 patients were further examined by diagnostic FS-ABR, with only 11 being confirmed to have sensorineural hearing loss, four to have normal hearing and seven to have conductive hearing loss (Table 2). In the last screening test, 20 children failed (Table 1) and were referred for FS-ABR testing. Of these, ten had conductive hearing loss and ten had sensorineural hearing loss (Table 2). Thus, from 107 newborns with confirmed CZS, ten were diagnosed with SNHL from the first exam until the last FS-ABR, resulting in a cumulative incidence of 9.3% (ten out of 107).

The FS-ABR served to test for air and bone conduction, with no differences observed between them. The characteristics [20], type and degree (i.e., considering the mean of the two analyzed frequencies) of hearing loss are summarized in Table 3 and the latency values for their wave I and wave V ABR curves are resumed in Table 4. Bone conduction thresholds are omitted as they do not characterize conductive hearing loss. Cochlear microphonics were not observed in any cases of SNHL. Of the ten cases of SNHL identified by the end of this study, four of the affected children had been tested with a second FS-ABR between the ages of 13 and 24 months and a third FS-ABR between the ages of 25 and 36 months. Three children (patient numbers 4, 7 and 8 in Table 3) were not tested in the third year of life before the conclusion of this study; however, their second and third tests, which were undertaken in the first and second years, confirmed the first result.

In the SNHL group, six (75.0%) of the eight children with known head circumference at birth presented with severe microcephaly, defined as a head circumference of three SDs below the mean for newborn gestational age and sex according to the INTERGROWTH-21st Table [13]. In this same SNHL group, nine mothers (90.0%) self-reported rash during pregnancy, with seven (77.8%) of these experiencing rash in the first trimester. However, there were no significant differences in characteristics or medical history between the children with and without SNHL (Table 5). At the end of the third year, none of the 107 children presented delayed-onset or progressive hearing loss over time.

4. Discussion

From an initial population of 138 children with IgM evidence of ZIKV infection at birth, 107 children fulfilled the eligibility criteria for the current study and were evaluated for sensorineural hearing loss during the first three years of life. During the follow-up period, ten children presented with sensorineural hearing loss, resulting in a cumulative incidence of 9.3%. Among children with SNHL, their mean age at the first hearing evaluation was 4.2 months.

In this population of children with confirmed congenital ZIKV infection, the frequency of hearing loss is higher than that found at birth in the general population, for whom the estimated prevalence of congenital hearing loss is 1.7/1000. If children with risk indicators for hearing loss are considered, this frequency can increase up to ten fold [18, 21].

Table 4. Latency values in milliseconds for wave I and wave V ABR curves.

Case No.	ABR	Last click (80 dB nHL) ABR latencies			
		RE		LE	
		I	V	I	V
1	Bilateral moderate SNHL	NR	NR	NR	6.73
2	Unilateral moderate SNHL (RE)	1.46	5.79	1.73	5.32
3	Bilateral SNHL (moderate on right / mild on left)	NR	5.94	NR	5.37
4	Bilateral profound SNHL	NR	NR	NR	NR
5	Unilateral mild SNHL (LE)	1.41	5.16	1.41	5.21
6	Bilateral moderate SNHL	1.36	5.06	1.46	5.16
7	Unilateral profound SNHL (RE)	NR	NR	1.52	6.31
8	Bilateral moderate SNHL	1.8	6.0	1.8	5.9
9	Unilateral moderate SNHL (LE)	1.67	5.58	1.73	6.20
10	Unilateral severe SNHL (RE)	NR	NR	1.67	5.53

Abbreviations: ABR = auditory brainstem response; RE = right ear; LE = left ear; dB nHL = decibels normalized hearing level; SNHL = sensorineural hearing loss; NR = no response.

Table 5. Characteristics of children with congenital Zika syndrome (N = 107), with and without sensorineural hearing loss.

Characteristics (number with information available)	Sensorineural hearing loss		p-value
	Yes (N = 10) n (%)	No (N = 97) n (%)	
Degree of microcephaly	**(N = 8)**	**(N = 80)**	
Severe (>3 SD below mean for gestational age)	6 (75.0)	36 (45.0)	0.399 *
Other (< = SD below mean for gestational age)	2 (25.0)	44 (55.0)	
Gestational age at birth	**(N = 9)**	**(N = 87)**	
<37 weeks (preterm)	1 (11.1)	11 (12.6)	1.000 *
37-41 weeks (term)	8 (88.9)	75 (86.3)	
> =42 weeks (postterm)	0 (0.0)	1 (1.1)	
Weight x GA	**(N = 9)**	**(N = 87)**	
SGA	2 (22.2)	13 (14.9)	0.534 *
AGA	6 (66.7)	68 (78.2)	
LGA	1 (11.1)	6 (6.9)	
Self-reported rash during pregnancy	**(N = 10)**	**(N = 85)**	
Yes	9 (90.0)	62 (72.9)	0.443 *
No	1 (10.0)	23 (27.1)	
Timing of rash during pregnancy	**(N = 9)**	**(N = 61)**	
First trimester	7 (77.8)	42 (68.8)	0.734 *
Second trimester	2 (22.2)	12 (19.7)	
Third trimester	0 (0.0)	7 (11.5)	
NICU	**(N = 7)**	**(N = 62)**	
Yes	0 (0.0)	5 (8.1)	1.000 *
No	7 (100.0)	57 (91.9)	
Infant sex	**(N = 10)**	**(N = 95)**	
Female	2 (20.0)	50 (52.6)	0.093 *
Male	8 (80.0)	45 (47.4)	
Infant death	**(N = 10)**	**(N = 95)**	
Yes	0 (0.0)	1 (1.1)	1.000 *
No	10 (100.0)	94 (98.9)	
	Mean ± SD	**Mean ± SD**	
Head circumference at birth (cm)	28.90 ± 2.77	29.12 ± 2.34	0.786 **

(*) Fisher's Exact Test (**) Student's t Test

Abbreviations: SD = standard deviation; GA = gestational age at birth; SGA = small for gestational age; AGA = appropriate for gestational age; LGA = large for gestational age; NICU = neonatal intensive care unit.

This observed prevalence of SNHL is also 1.6 fold higher than the 5.8% SNHL frequency found in our previous 2016 study involving a separate, smaller sample of children with congenital ZIKV infection who were only assessed at one time point in the first year of life [4].

Although the mean age of diagnosis of hearing loss in this group of ten children with SNHL was 4.2 months, all of them were diagnosed in their first year of life, and no child considered normal on the first examination failed any subsequent tests in this study, which supports the idea that the cause of hearing loss in these patients could have been congenital. Overall, the findings from the present study reinforce the recent inclusion by the Joint Committee on Infant Hearing [18] of Zika virus as a risk factor for early childhood hearing loss and underscore the importance of monitoring the development of affected children.

Among the children with detected hearing loss of any type, seven (38.9%) children at the first exam and ten (58.8%) children at the last exam were found to have conductive hearing loss. Conductive hearing loss is frequently found in infants, and similar proportions of conductive hearing loss have been reported in other populations; thus, one cannot relate this type of deficit with Zika virus infection. For example, a retrospective analysis of 27,935 neonates born at a university hospital in

Poland and evaluated as part of the universal neonatal hearing screening program reported a hearing deficit in 109 children, of whom 56 (51.4%) presented with conductive hearing loss [22]. In another study in the United States of America, the clinical records of 85 infants with suspected middle ear pathology were also retrospectively reviewed, and 51/85 (60%) were found to have been diagnosed with at least a unilateral middle ear effusion [23].

In the current study, 11 children were identified with sensorineural hearing loss in the first year of life, although one was considered to be normal after a second and third FS-ABR, leaving ten cases of SNHL at the conclusion of this study. The child who later tested normal had undergone a total of six FS-ABR assessments; after the first test for hearing loss at five months of age, the FS-ABR normalized at 14 months of age and remained normal through the last FS-ABR at 31 months of age. Furthermore, this child was born at term, with an appropriate weight for gestational age, and rash was self-reported by the mother during the second trimester of pregnancy. No factors were found that could explain the normalization of the FS-ABR in this case; thus, we hypothesize that the change in response could have resulted from the maturation process of the auditory pathways. Wave V is generated primarily within the inferior colliculus. It is also the most robust ABR wave and is used for electrophysiological threshold searches when studying auditory function. During the first years of life, peak latencies become progressively shorter in time and peak amplitude increases, becoming more visible at lower intensities [24]. Birth to three years of age is the critical period for development of wave V, which may explain the apparent hearing loss at birth that disappeared in subsequent tests [25].

Four children who did not pass the first Click-ABR actually had normal FS-ABR, possibly because broadband stimuli, such as click, stimulate practically the entire basilar membrane. Therefore, hearing losses in specific regions can be underestimated or even overestimated due to the different audiometric configurations [26]. Thus, FS-ABR is the most appropriate diagnostic procedure due to the frequency specificity of its stimuli, which leads to a better definition of the hearing status. Therefore, in order to accurately perform screening and diagnostic procedures, a combination of Click-ABR and FS-ABR was used in this study [27, 28, 29].

No specific patterns were observed concerning the degree or laterality of losses. All SNHL patients were treated with hearing aids and speech therapy, except for four patients who presented with unilateral hearing loss (patient numbers 5, 7, 9 and 10 in Table 3) and one patient (patient number 4 in Table 3) who received a cochlear implant because of profound bilateral sensorineural hearing loss.

It is important to state that no child considered normal on the first examination failed any subsequent exams. This finding provides evidence that, with respect to its long-term course, congenital Zika virus infection does not appear to present with progressive or delayed-onset hearing loss, as might be expected from infections with other TORCH agents [14, 15, 16]. Another Brazilian study conducted in the city of Rio de Janeiro from April 2016 to September 2017 revealed a rate of 5.1% of audiological alterations among the 78 children whose responses to automated brainstem auditory-evoked potential testing were evaluated in the first six months and at 12 months of age. This study similarly observed no progressive loss of hearing [9]. Overall, our findings align with the latest recommendations from the US Centers for Disease Control and Prevention (CDC) guidance for diagnosis, evaluation and management of infants with CZS, which no longer recommends a diagnostic ABR in the first year, if auditory screening is passed by automated ABR [30].

However, since knowledge on the pathogenesis of Zika virus in the auditory system remains limited and given that other viral congenital infections (e.g., rubella) have demonstrated delayed-onset hearing loss [14, 15, 16], even in the absence of viral reactivation, it would be reasonable to continue monitoring these children until at least 30 months of age. It has been recommended by the Joint Committee on Infant Hearing that children with risk factors for hearing loss should have a diagnostic auditory assessment by 24 to 30 months of age at the latest [18].

The exact site in the auditory system of the lesions caused by Zika virus is still uncertain [31], and the data presented herein do not clarify this issue [31]. Audiological tests addressing central auditory process assessment could provide useful information; however, the severe neuromotor disabilities often experienced by children with CZS represent a major limitation for investigating behavioral manifestations [32, 33]. Long latency ABR tests have also been used for this purpose, with the advantage of not being affected by neurological impairment, although definitive results are still unavailable.

Although 75.0% of the children with sensorineural hearing loss had severe microcephaly at birth, there was no statistically significant difference in the severity of microcephaly at birth between the groups with and without SNHL in this study. This finding differs from that of our previous publication, in which we reported that all of the children with SNHL were found to have severe microcephaly. This finding also differs from that of another study on visual impairment, in which the severity of microcephaly and the occurrence of maternal ZIKV infection in the first trimester of pregnancy appeared to be risk factors for ocular abnormalities [34]. Nevertheless, this information should be interpreted with caution due to the small sample size of the group with SNHL in our current study. Indeed, none of the studied variables were statistically significantly different between the groups.

The current study had strengths and limitations. Although it is the largest series ever published of hearing assessments in children with confirmed CZS, less than 10% of patients experienced SNHL. Due to the small sample size of children with hearing loss, the current study was unable to establish a precise presentation pattern for the hearing loss. Moreover, this case series is subject to potential selection bias, as only children with the most severe spectrum of CZS were referred for audiological follow-up and included in this study. Future investigations evaluating children with asymptomatic and milder presentations of CZS will be valuable to more fully understand the relationship between ZIKV and SNHL. Prospective pregnancy and birth cohort testing for maternal ZIKV infections, which are ongoing, will be critical for determining the overall frequency of SNHL among prenatally ZIKV-exposed children.

5. Conclusions

Sensorineural hearing loss is a clinical feature of congenital Zika syndrome. The findings of this study provide evidence that SNHL seems to be present since the time of birth with no delayed-onset manifestations or progressive decline in hearing. The mechanisms of hearing impairment, such as auditory cortex damage and subsequent central hearing processing, remain unclear and warrant further investigation. Additional studies using image assessment and electrophysiological assessment of the auditory pathways and the auditory cortex (e.g., to investigate the auditory evoked long latency potentials and central auditory processing) are needed to better clarify the topography of hearing loss in congenital Zika syndrome.

Declarations

Author contribution statement

Lilian F. Muniz and Mariana C. Leal: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Danielle S. Ramos: Conceived and designed the experiments; Performed the experiments; Wrote the paper.

Kátia M. G. Albuquerque, Ângela C. Leão and Marli T. Cordeiro: Conceived and designed the experiments; Performed the experiments.

Vanessa Van Der Linden: Conceived and designed the experiments.

Enny S. Paixão: Conceived and designed the experiments; Analyzed and interpreted the data.

Silvio S. Caldas: Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the paper.

Elizabeth B. Brickley: Contributed reagents, materials, analysis tools or data; Wrote the paper.

Rebeka J. F. Maciel: Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Gabriella G. S. Leitão: Performed the experiments.

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Data availability statement

Data included in article/supplementary material/referenced in article.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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