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Original articles

Encoding of speech sounds with frequency-following response in infants with Congenital Zika Syndrome: A case-controlled study

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ABSTRACT

Purpose: to investigate the frequency-following response (FFR) for sustained neural activity.

Methods: 39 individuals, aged between 20 to 47 months old were divided into 2 groups: (i) 20 individuals without prenatal exposure to the congenital Zika syndrome (CZS) or hydrocephaly, normal development, no risk factors for hearing loss or syndromic hearing impairment and (ii) 19 individuals diagnosed with CZS and microcephaly - based on imaging studies linked to the clinical presentation of the condition. All participants exhibited normal click-ABR tests. FFR waveforms were documented using the /da/ syllable employing the Navigator Pro. The statistical analysis used was ANOVA (p-value <0.05).

Results: no distinctions were observed concerning the variables of group, age, or gender with respect to FFR latency values, except for an interaction between gender and group for latency values associated with waves V and F. Children with CZS and microcephaly showed a difference for latency values in wave V for both males and females, when compared to the control group.

Conclusion: children presented with CZS and microcephaly showed higher average latencies for waves V, A, C, D and F (male) compared to the control group, whereas, in waves E, F (female) and O they showed higher values in the control group.

Keywords: Hearing; Zika Virus Infection; Microcephaly; Child; Speech Perception

INTRODUCTION

There are many other pathologies and pre, peri and post-natal events that can affect the central auditory nervous system, therefore, infants with risk indicators for hearing impairment should be monitored frequently as they may have speech, language, and hearing impairments[1,2].

The Zika virus infection was identified in Brazil in 2015–16, spreading to several regions of the country, mainly in the Northeast. During this period, the increased prevalence of neonatal microcephaly and other neurological malformations began to be associated with Zika virus infection in pregnant women[3].

Congenital Zika syndrome (CZS) infection has been associated with changes such as neonatal microcephaly, calcification in the subcortical parenchyma and thalamic areas[4] in addition to a wide spectrum of neurological (hyperreflexia, irritability, tremors, seizures), ophthalmological, and orthopedic changes (such as clubfoot or arthrogryposis)[5-7]. Other abnormalities such as including but not limited to brain atrophy and asymmetry, abnormally formed or absent brain structures, hydrocephalus, and neuronal migration disorders have also been related to CZS infection[7].

However, the hearing aspects of CZS have not yet been fully clarified. Studies of hearing acuity point to the presence of both peripheral hearing disorders[5-10] or normal hearing[11]. Other authors[12] point out that in patients with CZV, sensorineural hearing loss can be considered a clinical feature. And that the hearing loss seems to be present at birth and no change or worsening of the auditory condition has been observed. A study[13] documented a scenario of hearing impairment in an infant afflicted with CZS, who spent five days in intensive care due to neonatal seizures, necessitating oxygen therapy, and experienced early sepsis. Additionally, following an 11-day hospital stay, a diagnosis of microcephaly was established, and at the age of 12 months, computed tomography revealed hydrocephalus, accompanied by calcifications in the subcortical region, basal nuclei, cerebellum, and brainstem. In this instance, the outcomes of the frequency-following response (FFR) indicated the presence of all components, albeit with prolonged latency and diminished amplitude, potentially attributable to the reduced synchronization of neuron populations in the correlogram and FFR responses. This damage could be explained, since researchers have proven that the maturation of speech sounds occurs from the initial days of life[14] and depends on central nervous system (CNS) integrity[15], however, the deprivation of auditory input due to hearing loss can lead to low neural activity.

Another group of researchers performed the FFR evaluation on children exposed to CZS (with and without microcephaly) and the results showed values like those obtained with children with typical development[16]. It should be noted that researchers have confirmed the presence of neurophysiological changes in individuals exposed to other neonatal infections, such as congenital toxoplasmosis. The infants afflicted with toxoplasmosis exhibited elevated reactions in the latency measurements of waves V, A, E, F, and O waves, and diminished reactions in wave amplitude measurements A and F[17]. Another study showed that there seems to be damage in the FFR responses in individuals with auditory neuropathy, but only in the condition in which there is the presence of competitive noise[18].

Electrophysiological assessments do not necessitate input from the infant, nor demand continual vigilance, conscious awareness, motor responsiveness, or other advanced cognitive capabilities. They offer an impartial and non-intrusive evaluation, allowing researchers to deduce findings from an infant in the initial phases of life. While there is a wealth of literature chronicling ABR reactions in infants, only a limited number have concentrated on the functional arrangement at the subcortical level. The ABR with click stimuli is an excellent tool to assess how the auditory nerve and brainstem respond to sounds, bringing information about the functional status of the cochlea and auditory nerve[19].

The FFR is an auditory evoked potential, elicited by complex sounds, that reflects synchronous neural phase locking to the spectro-temporal components of the acoustic signal in the ascending auditory system[20,21], with contributions from both subcortical and cortical structures[22] and it is a good indicator how consonants and vowels, which are fundamental for good communication, sound encoding and language development, are processed[20].

The FFR is emerging as a hopeful instrument for evaluating the neural encoding of speech sounds in both healthy and clinical groups[23]. Therefore, this case control study included 19 infants up to 24 months old with congenital Zika syndrome and hydrocephaly and aimed to investigate the frequency-following response (FFR) for sustained neural activity.

METHODS

Ethical declaration

The study was approved by the Ethics Committee of Fundação de Apoio ao Ensino, à Pesquisa e à Extensão – FURNE, Brazil, (number 2.839.838 / CAEE 2888616.4.0000.5693). All individuals responsible for the infants were duly briefed about the study's intentions and methods, and those who agreed provided their informed authorization for inclusion prior to the children's participation in the research.

Participants

A total of 39 infants, comprising 27 females, aged between 20 and 47 months, were divided based on the inclusion criteria detailed below.

a) Control Group (CG): comprised 20 infants (14 females) without risk factors for hearing loss, without hearing impairment, complaint of learning or speech disorder who were selected from an Otolaryngology private clinic in Campina Grande, Paraíba, Brazil.
b) Congenital Zika Syndrome (CZS) group: comprised 19 infants (13 females) diagnosed with CZS through imaging studies, along with clinical manifestations such as microcephaly, excessive nuchal skin, irritability, alterations in muscle tone, and delayed motor development. These infants were receiving care at a facility specializing in microcephaly and Zika virus infection treatment in Campina Grande, Paraíba, Brazil.

The eligibility criteria applicable to CG and CZS comprised a normal click-ABR (absolute and interpeak values) response at 80 dB HL and normal middle-ear function, classified as type A tympanogram[24].

Procedures

Tympanometry

Tympanometry was performed in both ears with a 226 Hz probe tone using an Interacoustics AT 235h audiometer. The participants presented a type A tympanogram, suggesting normal middle ear function. The tympanogram classification followed the criteria proposed by Jerger[24].

Auditory Brainstem Response (click-ABR)

The ABR was recorded using BioMark software and recorded by the Biologic Navigator Pro System (Natus, Mundelein, IL). The active electrode was placed at the vertex (Cz), reference electrode at the ipsilateral mastoid, and the ground at the contralateral mastoid. The stimuli chosen were clicks with rarefaction polarity, presented to the right and left ears at 80 dB nHL (19.3 clicks/s, duration 0.1 ms, filtered 100–1500 Hz, 10.66 analysis window). Two collections of 2000 sweeps were collected to verify reproducibility. Waves I, III, and V were manually detected by the researcher and validated by an experienced observer, both unaware of the presentation group and analyzed according to the BioMark normative criteria. This procedure allowed the integrity of the auditory pathway up to the brainstem to be verified.

FFR

The FFR was conducted using identical electrode placement as that of click ABR and was recorded by the Biologic Navigator Pro Systems (Natus, Mundelein, IL) and analyzed by BioMark software. The stimulus used was the syllable [da] of 40 milliseconds (ms) duration, presented at 80 dB nHL monaurally to the right ear[25]. Two sets of 3000 stimuli were collected and the waves were summed, yielding a in a third waveform.

Stimuli were presented in alternating polarity at 10.9 stimuli per second, filtered at 100-2000 Hz with an 85.33 ms analysis window and alternate polarity. The initial peaks (V and A), the FFR peaks (C, D, E, and F), and the offset peak (O) were manually recognized by two experienced evaluators in FFRs who were unaware of the presentation group. The latency (ms) of each wave was measured and any peaks that could not be discerned were denoted as absent data were omitted from the data analysis.

Statistical analysis

A one-way analysis of variance (ANOVA) was employed to assess the differences in wave peak measurements across groups, with a focus on examining the impacts of age and gender and their interplays. Gender and age were regarded as independent variables, each having two categories. The ANOVA utilized a Snedecor F-distribution to assess whether there existed any notable distinctions among the factors or their interactions. The significance level was established at 5% ($p < 0.05$), and any statistically significant results were highlighted. The statistical analyses were executed using the R programming language (www.r-project.org).

RESULTS

Sample

From a total of 39 participants, 27 (69.2%) were females and 12 (30.8) were males. The mean age of participants was 35.9 ± 7.5 months old. After group division, the control group counted with 20 participants, 14 (70%) female and 6 (30%) males, aged between 22 to 47 months (35.1±6.5 months). While the CZS group consisted of 19 participants, 13 (68.4%) females and 6 (31.6%) males, aged between 20 to 49 months old, with mean age of 36.7±8.4 months.

Frequency-following response analyses

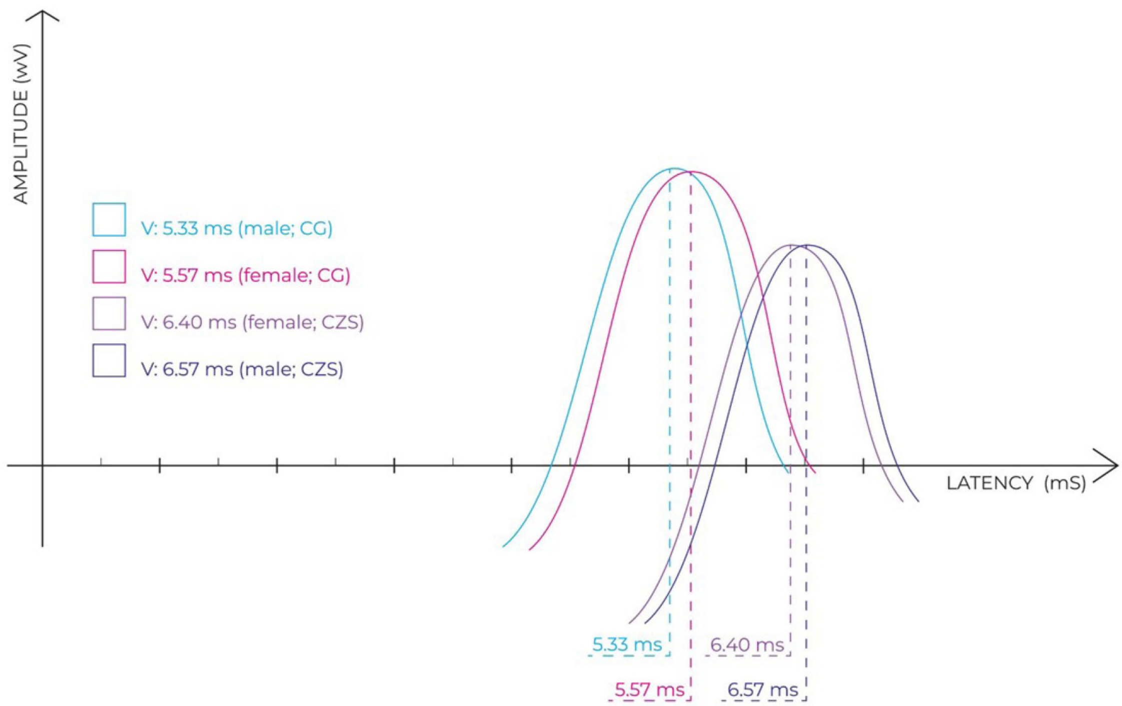
Results showed FFR latency values for both group analyses. The relationship between age and group did not show statistically significant responses for latency values for waves V (p-value: 0.817), A (p-value: 0.575), C (p-value: 0.541), D (p-value: 0.082), E (p-value: 0.82), F (p-value: 0.580) and O (p-value: 0.55). The other analyzed factor, gender, showed significant responses for wave V (p-value: 0.0349) and wave F (p-value: 0.034) latency values (Table 1, Figure 1).

When comparing the mean latency values between groups, it was found that the CZS group showed higher values for waves V (male p-value: < 0.001 ; female p-value: <0.001), A (p-value: 0.0555), C (p-value: 0.114), D (p-value: 0.731) and F (male p-value: 0.731) compared to the control group. The opposite was verified to average latency values for waves F (female p-value: 0.097), E (p-value: 0.469), and O (p-value: 0.771) who's the control group participants had higher latency values than the participants in the control group (Table 2).

Table 1. Comparison between groups and interaction of age and gender variables

FFR waves	V	A	C	D	E	F	O
Group x Sex	0.034*	0.468	0.143	0.883	0.302	0.034*	0.641
Group x Age	0.815	0.575	0.541	0.082	0.82	0.580	0.55
Age x Sex	0.528	0.801	0.651	0.681	0.528	0.082	0.95
Group x Age x Sex	0.921	0.612	0.36	0.469	0.177	0.570	0.755

*Statistically significant (ANOVA test).



Captions: CG: control group; CZS: congenital Zika syndrome, ms: milliseconds; μVmicrovolts.

Figure 1. Schematic and representative figure of wave V of the FFR between groups

Table 2. Latency values for waves V, A, C, D, E, F, and O were measured in control and study groups

Latency (ms)		CG (n = 20)				CZS group (n = 19)				p-value
		Average	SD	Min	Max	Average	SD	Min	Max	
Wave V	M	5.33	0.11	5.23	5.42	6.57	0.25	6.37	6.77	<0.0001*
	F	5.57	0.27	5.43	5.72	6.40	0.21	6.28	6.52	<0.0001*
Wave A		7.68	0.32	7.53	7.82	7.94	0.48	7.72	8.16	0.07
Wave C		18.26	0.30	18.12	18.39	18.47	0.48	18.25	18.69	0.114
Wave D		22.40	0.31	22.26	22.54	22.46	0.66	22.16	22.76	0.731
Wave E		30.92	0.44	30.73	31.12	30.79	0.65	30.50	31.09	0.469
Wave F	M	39.28	0.24	39.09	39.47	39.31	0.19	39.15	39.46	0.198
	F	39.42	0.35	39.23	39.61	39.17	0.53	38.88	39.46	0.097
Wave O		48.22	0.44	48.03	48.42	48.15	1.04	47.68	48.62	0.716

Captions: CG: control group; CZS: congenital Zika syndrome, SD: standard deviation, Min: minimum value, Max: maximum value, M: male, F: female, ms: milliseconds.
*Statistically significant (ANOVA test)

DISCUSSION

FFR is useful for monitoring changes in speech perception at the subcortical level, in addition to addressing issues related to impaired auditory processing and neurological development in specific populations, maturational changes, and sexual differences in auditory function.

FFR and gender

The difference between gender in the auditory system and its interaction with auditory processing is already well documented. For example, females generally have earlier and more robust responses than males to speech components[26]. Some theories have been proposed to explain the difference between neural responses to speech between males and females, including (i) differences in head size[27,28] (ii) differences in processing acoustic stimuli in the cortex; and (iii) the role of estrogen in the auditory system[26]. Differences were observed regarding sex for waves V and F latency values, but only in the group of children with CZS, the female group showed better responses as indicated in the literature. In the control group, variations in the V and F wave measurements were also observed, but with earlier responses in the male group, this result disagrees with findings in the literature. For example, one study found that healthy young adult females demonstrated significantly earlier FFR peaks (waves V and A) compared to males[26]. However, another longitudinal study found that gender differences are a continuous distribution and depend on development. The responses of children aged 3 and 5 years are similar between genders, with differences only in peaks V and A. In adolescents aged 14 to 15 years, however, the responses of males and females are noticeably different, and in adults aged 22 and 26 years, there are differences in all waves[26].

Analysis of FFR´s waves

The CZS group showed longer latency values (waves V and A) than the values found in the control group. However, it should be noted that statistically significant values were found only for wave V latency values, both for females and males. A study performed in 2021 with prenatal exposure to the CZS reported that there were no differences between the groups studied (CZS children and typical development without exposure to CZS) for the values of waves V and A[16]. The ages of the children selected in both studies are very similar. In other article[16], children with CZS were between 39 and 51 months old, while in the present study the age was 29 and 41 months. It should be noted that all children in our study presented responses in the ABR click within normal limits, ensuring auditory integrity up to the region of the lateral lemniscus, that is, the brainstem.

The wave V of the FFR evaluation is responsible for processing consonant sounds that are essential for the process of differentiating the meaning between words, thus, the alterations shown in this article can cause impairment in speech comprehension processes. It should also be noted that the present study was carried out in an ideal listening condition, therefore, without the presence of competitive noise. Therefore, it would be extremely important to accompany these children to monitor their school performance to understand what these identified alterations can bring about in terms of the learning process. Learning a language requires the child to analyze its acoustic environment. However, for this to occur it is essential that the child's central auditory nervous system is intact and working effectively. The children with CZS tested in the present study showed changes in the initial part of the FFR responses, indicating a defect in analyzing the sound stimulus, and this might cause difficulty in decoding sound and its meaning, leading to difficulties in communication and learning.

Besides that, the findings of wave V delays have also been found in children with the presence of neurophysiological changes in individuals exposed to other neonatal infections, such as congenital toxoplasmosis, autism spectrum disorder, dyslexia, and auditory neuropathy[17,18,30-33]. This deficit might be associated with behavioral difficulties agreeing with the findings of other researchers[16] who propose that prenatal exposure to the Zika virus may disrupt auditory development.

Concerning analysis of wave C, no significant statistical results were found between the groups. Wave C represents the transition between the consonant and the vowel, and to adequately process this segment, the individual must recognize rapid changes in the sound encoding. The absence or modifications in this wave may denote temporal processing issues, which are connected to nonlinguistic aspects of speech[34].

What does it refer to analysis of waves D, E and F did not find statistically significant values between the groups. The wave D stands for fundamental frequency (F0), for a speech sound, this corresponds to the rate at which the vocal folds vibrate and the neural response to the F0 is very rich[35]. Studies have shown that earlier values of D wave latency would be related to a better ability to recognize speech sounds. Autistic individuals, children with scholastic difficulties, children with otitis media, children with developmental language disorder have proven impairments in the amplitude of the fundamental frequency, which is directly related to the values of the wave D[36-38]. There are authors who point out that the process of attention to sound is conditioned by F0 responses[39], the waves E and F represent the harmonic portion of the stimulus. The harmonics represent whole-number multiples of the fundamental frequency (F0), typically reaching frequencies in the range of 1.2-1.3 kHz. In the context of a speech stimulus, specific harmonics known as formants hold significant phonetic relevance[35]. Other researchers[38] reported that children with developmental language disorder presented significantly higher first formant (F1) amplitudes what could explain the impairment in temporal accuracy during subcortical sound encoding, resulting in challenges in speech perception. Thus, children with CSZ with microcephaly, in this present study, seem to respond similarly to the control group.

And finally, the children with CZV and microcephaly were not statistically significant values between the groups. This way, children with CSZ with[40] microcephaly seem to present responses like their peers regarding the perception of the finalization of sound vocalization[40].

The results of this research made it possible to understand that children evaluated with CSZ and microcephaly could present an impairment in coding of speech. The coding of spectral cues is an aspect of auditory development that is important for speech perception and language development[22], since the timing of these neural responses conveys information about neural synchrony[33] and the FFR seems to be a viable instrument to understand these aspects.

In the present study, the temporal aspects of the FFR were analyzed. Future research could encompass examinations of additional frequency elements, like response timing, amplitude, and accuracy metrics, along with the fundamental frequency and its harmonics. There are some ways of improving the present research in the future. Our methodology consisted of a cross-sectional study of patients with CZS, conducting longitudinal studies in this population in addition to joining efforts for multicenter studies may help to better understand the findings in this population over the years of life, with a larger sample.

Until now, the works have been controversial, but there is a consensus in the sense that these children need to be evaluated by means of behavioral and electrophysiological methods. In addition, monitoring these changes could be important in studying and determining whether these changes in the development of neural networks are maintained, expanded, or even mitigated.

CONCLUSION

Differences in responses were observed among control and CZS groups. It was observed that the average latencies of the CZS group were higher for waves V, A, C, D and F (males) as compared to the control group, whereas, in waves E, F (females) and O, the values were higher in the control group. Thus, new studies should be carried out for these findings to be understood with greater accuracy and even observed whether these responses will be maintained in a larger number of children with CZS analyzed.

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