Auditory Neural Responses and Communication Function in Children with Prenatal Exposure to the Zika Virus

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INTRODUCTION

The overarching theoretical framework for this research is that prenatal virus exposure can adversely impact auditory neurodevelopment and language outcomes, even when peripheral hearing is normal.

Prenatal exposure to the mosquito-borne Zika virus during the 2015-2018 epidemic in Brazil was associated with an increased number of infants born with microcephaly (Congenital Zika Syndrome, CZS). These most severely affected cases presented with multiple neuro-developmental concerns involving communication, cognition, visual, and motor function[1]. However, the CZS cases comprised only ~10% of the exposed children.

The developmental consequences of prenatal Zika virus exposure in children who appeared asymptomatic at birth are less well known, but recent studies report difficulties in language and communication emerging after 12 months of age in 30+% of the exposed toddlers[2]. Their cognitive and motor functions remained in the typical range[3].

These high rates of language delays contrast with the low incidence of peripheral hearing loss[4], suggesting that factors other than peripheral hearing, such as auditory neural processes, must be considered.

The auditory brainstem response (ABR) and cortical auditory evoked potentials (CAEPs) provide objective metrics of subcortical and cortical neural function, from sound onset detection to identification and differentiation, which are important abilities for optimal communicative and language development.[5]

The goal of this study was to systematically characterize auditory neural function and communicative abilities in children with prenatal exposure to the Zika virus compared to unexposed controls matched on age, sex, ethnicity, and socioeconomic status.

METHODS

- Positive / negative history of prenatal Zika virus exposure confirmed at birth by laboratory testing (RT-PCR) or established epidemiologic criteria.
- Exclusion criteria: Genetic syndromes, head injury, prenatal dengue or chikungunya exposure, and family history of SNHL or language disorders.
- Peripheral auditory evaluation: Otoscopy, tympanometry, otoacoustic emissions, behavioral audiometry or ABR threshold search.

Auditory Evoked Potential Test Parameters

	ABR	CAEP
Stimuli	Click (100-µsec); Rarefaction polarity	/ba/, /da/, /ga/ (290-305 ms) digital recordings Female native speaker Brazilian Portuguese.
Intensity	75 dB nHL	75 dB nHL
Rate	21.7/s, 61.7/s	0.7/s
Filter	30 – 3000 Hz	0.1 – 30 Hz
Sweeps	3000	75 per syllable
Transducer	ER3 Insert earphones- Monaural stimulation	Sound field- Speaker 1 meter in front of participant
Electrode Montage	2 channel (Cz-A1, Cz-A2, Fpz ground)	

Behavioral Assessments

- *Communication* abilities in daily life were evaluated using Vineland Adaptive Behavior Scales, 3rd Edition (VABS), a standardized caregiver report appropriate for use in populations with developmental disabilities (e.g., CZS) or typical development.
- *Receptive vocabulary:* Peabody Picture Vocabulary Test (PPVT), 3rd Edition
- *Expressive vocabulary:* Picture Naming Test (PNT) for Children and List of Evaluation of the Expressive Vocabulary (LAVE)
- *Phonological processing: Child Language Test (ABFW)*
- *Cognitive Function: Columbia Mental Maturity Scale (CMMS),* 3rd Edition and *Wechsler Nonverbal Scale of Ability (WNV)*

All measures were administered in Brazilian Portuguese.

RESULTS

Participants

Group	n	Age (years)	Head Circumference (cm)	Ethnicity[1]	Socioeconomic Status (BECC[2])	Communication (VABS[3])
CZS	25 (11 female)	5.93 ± 0.62	44.73 ± 3.74	Black: 3, Brown: 6, White: 16	21.50 ± 7.32	30.43 ± 19.14
Exposed	117 (49 female)	6.29 ± 0.42	51.86 ± 2.00	Black: 11, Brown: 47, Amarela: 1, White: 54, No report: 4	25.66 ± 9.09	80.51 ± 13.70
Control	90 (43 female)	5.54 ± 0.95	51.87 ± 1.65	Black: 5, Brown: 31, Amarela: 1, White: 51, No report: 2	28.88 ± 8.60	89.94 ± 14.60

[1] The labels listed represent the terms used by the Brazilian Institute of Geography and Statistics.
[2] Brazilian Economic Classification Criteria: low = 0 - 16, high = 45 - 100, median = 23 - 28
[3] Vineland Adaptive Behavior Scales: standard score M=100, SD=15

Behavioral Assessments

Measure	Exposed	Controls	p-value
PPVT (Total)	49.24 ± 17.33	44.26 ± 16.14	**0.038**
PNT (SS)	106.46 ± 18.55	118.65 ± 20.49	**<.001**
LAVE (Total)	290.18 ± 28.62	287.20 ± 34.71	0.506
ABFW (SS)	92.58 ± 12.28	89.38 ± 14.72	0.100
Columbia MMS (SS)	104.02 ± 12.78	106.55 ± 15.29	0.209
Wechsler Nonverbal (SS)	90.37 ± 16.68	101.38 ± 14.83	**<.001**

SS – Standard Score

CZS (Microcephaly): Subcortical and cortical responses present but altered[6]

a) ABR

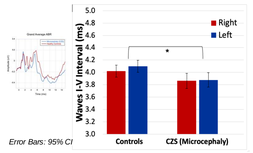

Figure 1a. *Wave V absolute and Waves I-V interwave latencies are significantly shorter in CZS vs. age- and sex-matched controls (F(1,36) = 11.459, p < .001, η_p^2 = .241 and F(1,33) = 7.699, p = .009, η_p^2 = .189). No group difference for Wave I latency (p=.269).*

b) Grand-average CAEP

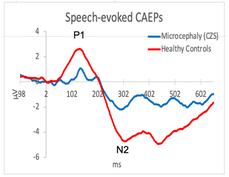

Figure 1b. *P1 latency is delayed in CZS compared to controls (F(1,38) = 4.774, p = .035, η_p^2 = .114). N2 amplitude is smaller (F(1,38) = 4.711, p = .036, η_p^2 = .113) and latency is shorter in CZS vs. controls (F(1,38) = 15.639, p < .001, η_p^2 = .292).* No group differences in *P1 amplitude (p>.05).*

c) Speech Sound Differentiation (CAEP)

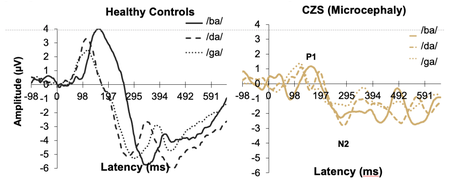

Figure 1c. The control group showed slower P1 latencies in response to /ba/ versus /da/ or /ga/ (paired t(24) = 7.196, p < .001, d = 1.44, and t(24) = 4.391, p < .001, d = 0.88), while no between-sound differentiations were observed within the CZS group at P1. Speech sound differentiation was indicated by longer N2 latencies in response to /ba/ versus /da/ or /ga/ (t(40) = 2.675, p = .011, d = .42, and t(40) = 3.366, p = .002, d = .53), with no significant group differences.

Longer (more typical) Wave V latencies were significantly associated with higher VABS communication skills in CZS: *r* = .596, *p* = .012.

Larger P1 amplitude difference for the /ba/-/da/ contrast was associated with higher VABS communication skills in CZS: *r* = .606, *p* = .028 (controlling for head circumference).

Exposed children: Subtle CAEP differences in speech sound differentiation

a) ABR

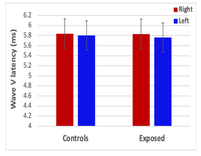

Figure 2a. No group differences in Wave I or Wave V latency (mean and one standard deviation).

b) Grand-average CAEP

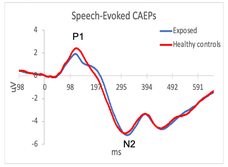

Figure 2b. No group differences in P1 or N2 amplitude or latency.

c) Speech Sound Differentiation (CAEP)

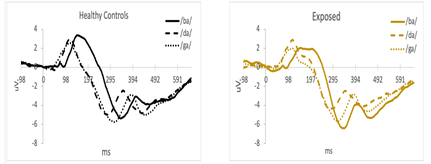

Figure 2c. *The control group generated larger P1 amplitudes for /ba/ than /da/ and /ga/ (paired t(79) = 3.314, p < .001, d = .370, and t(79) = 3.385, p < .001, d = .378). The exposed group differentiated speech sounds at the later N2 stage, with larger amplitude for /ba/ than /da/ (paired t(107) = -2.686, p = .008, d = .258). Both groups exhibited slower P1 and N2 latencies in response to /ba/ vs. /da/ or /ga/ (all p < .001, d = .374 - .997, with no significant between-group differences.*

Larger P1 and N2 amplitude differences for the /ba/-/da/ and /ba/-/ga/ contrasts in the control group were associated with higher PPVT and VABS communication scores: *r* = .250 - .302, *p* = .009 - .045. Reduced N2 latency difference for the /ba/-/ga/ contrast correlated with better LAVE scores in the exposed group: *r* = - .212, *p* = .037. In both groups, the analyses controlled for nonverbal ability (WNV).

DISCUSSION

Despite similar peripheral hearing for all groups, the CZS and exposed groups demonstrated lower adaptive communication abilities and altered auditory neural function at subcortical and/or cortical levels.

- **Microcephaly related to CZS is associated with alterations in subcortical and cortical auditory neural function.**
  - Reduced ABR latencies in the CZS group differ from previous reports, possibly due to the older age of this cohort, direct comparison to matched controls, and careful assessment of peripheral auditory function.
  - Shorter than typical ABR absolute and interwave latencies have been observed in other populations with neurodevelopmental disabilities [7,8] and auditory processing difficulties.[9,10]
  - Cortical speech sound detection and differentiation are present but reduced in children with microcephaly.
  - These results suggest altered temporal coordination of consecutive auditory processing stages and reduced number of cortical neurons firing in temporal synchrony following the speech sound onset.
- **Exposed children (without microcephaly) demonstrate typical subcortical function but altered cortical speech sound differentiation.**
  - At the group level, the exposed group performed in the average range on direct behavioral measures of discrete abilities relevant to communicative functioning (phonological processing, receptive / expressive language, nonverbal IQ). Only adaptive communication in daily life fell significantly below average.
  - There was no evidence of atypical subcortical or cortical auditory responses that index sound onset detection.
  - Differences from typical controls were observed in the amplitude of cortical auditory responses indexing speech sound differentiation, suggesting delayed stimulus categorization (at the N2 vs. P1 stage). Similar delays have been previously reported in children with language and communication difficulties due to other neurodevelopmental conditions.[11]
- The associations between communication performance and subcortical and/or cortical neural responses observed in both exposure groups (with and without microcephaly) highlight the value of auditory evoked potentials in assessing clinical populations at risk for neurodevelopmental disabilities. The ability to identify individual differences in specific auditory processing functions informs clinical management and allows for design of targeted interventions.

Longitudinal follow-up of children with prenatal Zika virus exposure is currently carried out in our ongoing research (NIH-NIDCD R01 DC021698) to better characterize the risk for further communication delays.

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