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# Microcephalic Children Exposed To Zika Virus And Other Infectious Agents During The Intrauterine Period: Auditory Findings In A Case Series

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***Abstract:***
***Background****: This study aimed to describe the auditory findings of microcephalic children exposed to Zika virus and other infectious agents during the intrauterine period. In this article, we present the cases of 8 microcephalic children aged 5 to 7 years were born between September 2015 and February 2018.*
***Materials and Methods****: The audiological evaluation consisted of Acoustic Immittance measurements, Transient Evoked Otoacoustic Emissions (TEOAE), Auditory Brainstem Response (ABR), and Auditory Steady State Response (ASSR). The mean age was 77.25 ±9.5 months.*
***Results****: Most children (75%) presented type "A" tympanometry curve, acoustic reflexes and TEOAE absent in one or both ears. The ABR assessment was not completed in 25% of children. Five (62,5%) children presented responses with slightly reduced absolute latencies of wave V and one (12,5%) child had unilateral absence of responses. In the ASSR, this one (12,5%), presented findings compatible with severe hearing loss, four (50%) presented minimum levels of electrophysiological responses compatible with thresholds within normality and one (12,5%) child showed responses compatible with unilateral moderate hearing loss.*
***Conclusion:*** *This study described altered electrophysiological and electroacoustic auditory responses in microcephalic children exposed to Zika virus and to other TORCH agents and our results point to the need to evaluate and monitor microcephalic children with audiological assessment instruments throughout their lives, to detect hearing loss and provide interventions at the appropriate time.*
***Keywords:*** *Microcephaly; Hearing Loss; Children; Zika Virus.*

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## I. Introduction

Microcephaly is a neurological condition characterized by anomalies in the growth of the cranial circumference that may be evident at birth or postnatally[1]. Congenital microcephaly is caused by a multitude of drivers affecting maternal-fetal health during pregnancy[2]. There is a well-established association between microcephaly and maternal infections, especially those occurring in the first 12 weeks of pregnancy[3]. Until 2015, the most common congenital infections were: syphilis, toxoplasmosis, rubella, cytomegalovirus, and herpes simplex virus, forming the acronym STORCH (Syphilis, Toxoplasma gondii, other, rubella virus, cytomegalovirus, herpes simplex virus)[4]. Between 2015 and 2016, the Zika virus (ZIKV), a Flavivirus transmitted by the bite of the Aedes mosquito caused an important epidemic in the Americas and brought the world's attention to links between Zika infection and microcephaly[5].

Zika virus (ZIKV), caused tissue lesions and deleterious consequences in children whose mothers were exposed to ZIKV during pregnancy, including neurological complications, serious complications compatible with Congenital Zika Virus Syndrome (SCZV)[6] such as changes in growth and development[7], fetal loss[8], disorders of swallowing [9], visual impairment[10], and hearing losses acquired and congenital due to the infection[11]. Congenital infections are the main factors related to microcephaly associated with hearing loss and the mechanism involved in the genesis of hearing loss is quite varied[12,13]. Recent study suggests that ZIKV infections cause congenital hearing loss by inducing progenitor cell death, and in the case of Human cytomegalovirus infection occur by disruption of critical developmental pathways[14].

Virus infections when arising during pregnancy can generate cochlear damage that can progress to sensorineural hearing loss[15]. In Brazil, the first report of hearing loss associated with SCZV was made in 2015[16] and microcephalic neonates exposed to ZIKV in utero have severe to profound unilateral and/or bilateral sensorineural hearing loss, with a prevalence between 5.1 and 75%[17-20]. In congenital an acquired hearing loss high prevalence and diagnosed hearing loss in asymptomatic children at birth points to the need to monitor children born to mothers exposed to ZIKV during pregnancy[21].

Considering the relevance of the clinical picture of children diagnosed with microcephaly and the high prevalence of hearing disorders in children exposed to congenital infections, all its clinical manifestations must be considered and studied. This study aimed to describe the results of the audiological evaluation of eight microcephalic children exposed to the Zika virus and other TORCH agents during the intrauterine period in the Brazilian Amazon between September 2015 and February 2018.

## II. Material And Methods

This is an observational case series study that describes the clinical characteristics and the auditory findings of microcephalic children who were exposed to ZIKV and other TORCH agents in the intrauterine period at any time during pregnancy. This research was approved by the Research Ethics Committee of the Tropical Medicine Foundation Doctor Heitor Vieira Dourado (CAAE nº 26743219.6.0000.0005, with approval number: 3.853.470). Mothers, parents, or legal guardians of the participants who agreed with the children's participation signed the Free and Informed Consent Form after the due explanations regarding the objectives and procedures of the study.

Maternal ZIKV infection was confirmed by serological test Anti-Zika Virus ELISA (IgG) (Vircell S.L., Spain) at the Central Public Health Laboratory in Amazonas (LACEN-AM) and mothers and children were tested between september and october of 2020 for infections by Treponema pallidum, Toxoplasma gondii, Rubella virus, Cytomegalovirus (CMV), Herpes simplex type 1 and 2 (HSV), Human immunodeficiency virus (HIV), Epstein–Barr virus (EBV), dengue virus (DENV) and Parvovirus B19 (PvB19) through IgG identification kits by ELISA (Euroimmun Brazil Medical Diagnostic) according to the manufacturer's protocol.

Children assisted at Policlinica Antônio Aleixo, a specialized care health unit, a reference in the public network for early stimulation and rehabilitation of children diagnosed with microcephaly in the city of Manaus, Amazonas were evaluated by two audiologists and a pediatric in a private clinic speech therapy and audiological evaluation and rehabilitation (Casa Caracol, Manaus, Amazonas). Information on maternal history, prenatal history, and birth was obtained through interviews with the mothers, in the pregnant woman's and child's health booklet.

The children's external acoustic meatus was submitted to inspection using a Pen-scope otoscope Riester. Children who had partial or total obstruction were referred for otorhinolaryngological evaluation and evaluated after medical management. The audiological evaluation consisted of electroacoustic procedures (Acoustic Immittance measurements and evoked otoacoustic emissions) and electrophysiological (Auditory Brainstem Response and Auditory Steady State Response). At Acoustic Immittance measurements (AIM), to verify the integrity of the tympanic-ossicular system, was used an immittance device model AT235 manufactured by Interacoustics. The tympanometric curves were classified according to Jerger[22] in type A curve (suggestive of normal mobility of the tympanic system ossicular), type Ar curve (suggestive of flaccidity in the tympanic-ossicular system); type B curve (suggestive of fluid in the middle ear) and type C curve (suggestive of a tubal dysfunction). Regarding the stapedial reflexes, they were performed with ipsilateral stimuli, at frequencies of 0.5Hz, 1.0kHz, 2.0kHz and 4.0kHz, due to the need for speed in performing the tests. They were considered altered when obtained at intensity above 100dBHL[23].

The TEOAE, to assess cochlear functioning, specifically outer hair cell integrity, were performed by transient stimulus at frequencies of 1.5kHz, 2.0kHz, 2.8kHz and 4.0kHz using the ILO equipment manufactured by Otodynamics, with click stimulus at an intensity of 75-83 dBpeSPL. TEOAE was considered present when the signal-to-noise ratio per frequency band was > 3 dB for 1.5kHz and > 6 dB for 2.0kHz, 2.8kHz and 4.0kHz in 3 consecutive frequency bands. Overall reproducibility considered was > 50% and probe stability > 70%. In the absence of these responses, absent otoacoustic emissions were considered[24].

The ABR, to verify the integrity of the auditory pathway, and the Auditory Steady State Response (ASSR), to assess hearing with frequency specificity and obtain minimum levels of response (NMR), in the Eclipse 25 equipment manufactured by Interacoustics was used. Initially, the skin on the forehead and mastoids was cleaned with abrasive paste (Nuprep®) to remove oiliness and facilitate the attachment of surface electrodes. Insert Ear-Tone 3A earphones and disposable surface electrodes (Meditrace) were used on the forehead Fz (active) and Fpz (ground) and on the right and left mastoids (M2 and M1). The electrode impedance was kept below 3Ω. For the examination, the child was in natural sleep or sedated, on the mother's lap or lying in a reclining chair.

To research ABR, the click stimulus was used, by air conduction, at an intensity of 80 dBnH, and the presence and absolute latencies of waves I, III and V, the interpeak intervals I-III, III-V and I-V, and the interaural difference of the absolute latencies of waves V, according to normality values for the age group. It was performed by bone route, with tone burst stimulus, when altered thresholds were detected. The parameters used for registration were presentation rate of 27.7/sec; 12ms window; 33-1500 Hz filter, with alternating polarity and 2000 stimulus. For the ASSR research, the examination conditions, the position of the electrodes and the type of earphone were the same used in the click-ABR. Bilateral multi-frequency stimulation was performed using NB chirps with frequencies of 0.5Hz, 1.0kHz, 2.0kHz and 4.0kHz presented at repetition rates around 80Hz. The minimum levels of electrophysiological responses were analyzed, with a correction factor by the manufacturer.

Descriptive statistics were used representing categorical variables in frequency and percentage, and continuous variables presented in mean and standard deviation[25].

## III. Result

Between January 2015 and September 2018, Amazonas reported 46 cases of microcephaly in newborns[26]. In 2020, 23 children received care from the multidisciplinary team at Policlínica Antônio Aleixo. Eighteen mothers were contacted, but only ten mothers accepted their children's participation in this study. One did not show up for all the exams to be carried out and one child died. Table 1 presents the socio-demographic and clinical characteristics of pregnant women and the birth, neonatal, and postnatal clinical characteristics of eight children with microcephaly exposed in utero to the Zika virus and other TORCH agents. The mean age of the mothers was 27±3.5years. The suspicion of ZIKV infection occurred in the 1st (4 women, 50%) and 2nd trimesters of pregnancy (4 women, 50%). The number of prenatal consultations was high, with an average of 10.1 ± 2.23 consultations. A single mother had a low number of consultations (5 consultations, case 3). None of the mothers used Tobacco, Alcohol or/and Illicit intake. Only one mother had a urinary tract infection (case 5). Of the mothers evaluated, all women had positive serological tests to the rubella virus which result may be related to the vaccine. And the other most common agent was CMV and HSV (Table 1).

**Table no 1:** Sociodemographic and clinical characteristics of pregnant women with positive serological test (IgG) for Zika virus and Birth, neonatal, and postnatal clinical characteristics of children exposed in utero to the Zika virus and other TORCH agents.

| Mothers information | | | | | Children information | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Case | Age, mean | NPC | Trimester of ZIKV infection | IgG present | Age, sex | Childbirth type | IgG present | G.A. | NICU stay >5 d | NHS |
| 1 | 28y | 10 | 1 | Rubella, HSV, CMV and PvB19 | 79m, M | Caesarean | Rubella and CMV | 38w | Yes | RE: Pass<br>LE: Pass |
| 2 | 31y | 10 | 2 | Rubella, HSV, CMV and PvB19 | 79m, M | Caesarean | Rubella, CMV and PvB19 | 40w | Yes | RE: Fail<br>LE: Fail |
| 3 | 23y | 05 | 1 | Rubella, HSV, CMV, PvB19 and Syphilis | 86m, M | Vaginal | TXM, Rubella and CMV | 38w | No | RE: NR<br>LE: NR |
| 4 | 24y | 10 | 2 | Rubella, HSV, CMV, and PvB19 | 90m, F | Vaginal | Rubella | 40w | No | RE: Pass<br>LE: Pass |
| 5* | 27y | 11 | 2 | Rubella, HSV, CMV and TXM | 79m, M | Caesarean | Rubella, CMV, TXM and PvB19 | 38w | No | RE: Fail<br>LE: Fail |
| 6 | 28y | 11 | 2 | Rubella, HSV, CMV and TXM | 62m, F | Vaginal | Rubella | 39w | No | RE: Pass<br>LE: Pass |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 7** | 32y | 12 | 1 | Rubella, HSV, TXM and Syphilis | 78m, F | Caesarean | Rubella | 39w | Yes | RE: Fail<br>LE: Fail |
| 8 | 23y | 12 | 1 | TXM, Rubella, CMV, HSV and PvB19 | 65m, M | Caesarean | Rubella and PvB19 | 38w | No | RE: Pass<br>LE: Pass |

y=years; m=months; M=male; F=female; w=weeks; TXM=Toxoplasmosis; HSV= herpes simplex virus 1 and 2; PvB19= Parvovirus B19, CMV= cytomegalovirus; G.A= Gestacional Age; NICU= Neonatal Intensive Care Unit, NHS=Neonatal Hearing Screening; RE=Right ear; LE=Left ear NR: not researched, d=days
* Fail in the NHS and didn't take the retest
** Fail in the NHS and pass in the retest.

Of the 8 children evaluated, three children were female (Cases 4, 6 and 7) with a mean age of 77.25 ±9.5 months (62-90 months). Most were born by cesarean delivery (63%). All evaluated children had an Apgar score greater than 7 (only one child was not evaluated due to home, Case 3). None of the children were premature and the gestational age averaged 38.8 ± 0.9 weeks. Only the case (case 5) has low birth weight (<2500 g) and hyperbilirubinemia (Case 2). Three children remained in the Neonatal Intensive Care Unit for more than 5 days (Case 1, 2 and 7) and one (case 8) had deafness in the family. After birth, seven children underwent hearing screening, cases 2, 5 and 7 failed, with case 5 not having a retest and case 7 passing the retest (table 1). All Children, at the time of evaluation, had IgG for different infection agents, with rubella (Cases 1,2,3,4,5,6,7 and 8), CMV (Cases 1, 2, 3 and 5) and PvB19 (Cases 2, 5 and 8), being the most common (Table 1).

The results of visual inspection of the external ear, revealed that most ears without obstruction. Two children (Cases 6 and 7) presented partial obstruction in one of the ears. Both were referred to otorhinolaryngological evaluation and after medical conduct returned to the audiological assessment.

Table 2 shows the results of the hearing evaluation tests performed. In AIM, about tympanometry, 06 (75%) of the children had a type "A" tympanometry curve in both ears (Cases 1, 2, 3, 4, 5 e 8), while 2 (25%) had a type "C" tympanometry curve in the right ear (Cases 6 and 7), suggestive findings of middle ear pathologies. As for acoustic reflexes, one (12.5%, case 7) had absent reflexes in one ear and 01 (12.5%, Case 3) had absent reflexes in both ears. Two children (25%, Cases 5 and 6) had no responses in one of the ears in the TEOAE assessment, and two (25%, Cases 3 and 7) had no responses in both ears. This absence of responses occurred mainly at lower frequencies, specifically in the 1 kHz frequency range.

**Table no2:** Audiological findings in children exposed in utero to the Zika virus and other infectious agents, Amazonas, Brazil.

| Case | Tymp | AR | TEOAE | ABR | ASSR | Summary of findings |
|---|---|---|---|---|---|---|
| 1 | RE: A<br>LE: A | RE: P<br>LE: P | RE: P<br>LE: P | RE: Al<br>LE: Al | RE: 0,5:10 / 1K:15 / 2K:15 / 4K:10<br>LE: 0,5:--- / 1K:20 / 2K:15 / 4K:10 | Objective exams are indicative of hearing sensitivity within normal limits |
| 2 | RE: A<br>LE: A | RE: P<br>LE: P | RE: P<br>LE: P | RE: Al<br>LE: Al | RE: 0,5:10 / 1K:15 / 2K:20 / 4K:15<br>LE: 0,5:05 / 1K:15 / 2K:20 / 4K:20 | Objective exams are indicative of hearing sensitivity within normal limits |
| 3 | RE: A<br>LE: A | RE: Abs<br>LE: Abs | RE: Abs<br>LE: Abs | RE: NR<br>LE: NR | RE: NR<br>LE: NR | Audiological findings are suggestive of hearing loss |
| 4 | RE: A<br>LE: A | RE: P<br>LE: P | RE: P<br>LE: P | RE: Nl<br>LE: Al | RE: 0,5:05 / 1K:05 / 2K:15 / 4K:10<br>LE: 0,5:05 / 1K:05 / 2K:10 / 4K:10 | Objective exams are indicative of hearing sensitivity within normal limits |
| 5 | RE: A<br>LE: A | RE: P<br>LE: P | RE: Abs<br>LE: P | RE: NR<br>LE: NR | RE: NR<br>LE: NR | Audiological findings are suggestive of hearing loss in right ear |
| 6 | RE: C<br>LE: A | RE: P<br>LE: P | RE: Abs<br>LE: P | RE: Nl<br>LE: Al | RE: 0,5:35 / 1K:30 / 2K:45 / 4K:45<br>LE: 0,5:--- / 1K:20 / 2K:15 / 4K:15 | Audiological findings are suggestive of hearing loss in right ear |
| 7 | RE: C<br>LE: A | RE: Abs<br>LE: P | RE: Abs<br>LE: Abs | RE:Abs<br>LE: Al | RE: 0,5:25 / 1K:70 / 2K:85 / 4K:85<br>LE: 0,5:05 / 1K:15 / 2K:20 / 4K:20 | Objective exams are indicative of sensorineural hearing loss in right ear confirmed by ABR bone-conducted tone burst |

| | | | | | | |
|---|---|---|---|---|---|---|
| 8 | RE: A<br>LE: A | RE: P<br>LE: P | RE: P<br>LE: P | RE: Al<br>LE: Al | RE: 0,5: --/ 1K:15 / 2K:20 / 4K:15<br>LE: 0,5:20 / 1K:15 /2K:25 /4K:10 | Objective exams are indicative of hearing sensitivity within normal limits |

RE=Right ear; LE=Left ear; Tymp= Tympanometry; A=type A, tympanometry normal curve; C=type C, tympanometry curve with negative pressure; P=present; Abs= absence of response; NR= Not researched; TEOAE= Transient Evoked Otoacoustic Emissions; ABR= Auditory brainstem response with click; Nl=absolute latencies of waves I, III and V and values of interpeak latencies within the normal range; Al=absolute latency of wave V reduced.

The ABR assessment was not completed in 25% of children (Cases 3 and 5) who were sedated, even after all the sleep re-strictions the night before, as instructed by the mothers and sedation attempt. Of the six children evaluated, five (62,5%, Cases 1, 2, 4, 6, and 8) children presented responses with slightly reduced absolute latencies of wave V and interpeak intervals within the normality standards for the age group and one child (Case 7) had absence of responses in the right ear and the type of sensorineural was confirmed by the register of ABR by bone-conduction with tone burst stimulus. In the ASSR, this one (12,5%, Case 7), presented findings compatible with severe hearing loss, four (50%, Cases 1, 2, 4 and 8) presented minimum levels of electrophysiological responses compatible with thresholds within normality and one child (12,5%, Case 6) showed responses compatible with moderate hearing loss in the right ear.

In summary, one case of hearing loss was confirmed (Case 7) and three remained as suspected hearing losses (Cases 3, 5 and 6).

## IV. Discussion

ZIKV infection is responsible for changes in the CNS that can be reflected in hearing loss, which compromises the quality of life of sufferers. Early identification of congenital hearing loss, especially in children exposed to ZIKV in utero, allows interventions that are essential to prevent delays in the development of speech, language, and cognitive behavior in children[27]. In this study, we evaluated the hearing of eight microcephalic children exposed in utero to ZIKV, whose mothers during pregnancy and the children during evaluation had positive IgG for agents causing TORCH syndrome. The children were evaluated through a battery of exams, including EOAE and PEATE. Both are important tools for early detection of childhood hearing loss and used soon after birth to screen for congenital hearing loss, diagnosis up to the third month of life and intervention, up to the sixth month, if necessary[28]. The frequency of audiological changes was 50% when 8 microcephalic children were evaluated, although only one case of hearing loss was confirmed (Case 7, 13%). However, it is interesting to consider that children and mothers were IgG positive for different infectious agents that may have been acquired during pregnancy and that have the potential to cause congenital deafness[29], therefore, the auditory changes evidenced cannot be exclusively caused by intrauterine exposure to ZIKV. Rubella, HSV, and CMV were the most common co-infections associated with hearing changes, although the only patient (Case 7) with confirmed hearing loss did not have CMV infection. Congenital CMV is the most common cause of nonhereditary sensorineural hearing loss in childhood with a global incidence of sensorineural deafness of around 12.6%[30].

Different studies have shown sensorineural hearing loss in children exposed in utero to ZIKV[20,31,32]. In Brazil, the first cross-sectional study with 69 babies with microcephaly caused by congenital infection confirmed by ZIKV, found that hearing loss was prevalent in 5.8% of patients evaluated with a mean age of 3.8 months[33]. A study in Colombia evaluated the hearing of 68 babies whose mothers developed symptomatic and confirmed Zika infection during pregnancy and found auditory changes in Brainstem Auditory Evoked Potentials in 8.8% of them[34]. We showed much higher rates of audiological alterations (50%), including sensorineural hearing loss (13%), even in children assessed at an older age. The changes affected one or both ears in the OEAT assessment, mainly at lower frequencies (1.0kHz). In two cases (6 and 7), the children presented an altered tympanometric curve (Type C) in the ear in which the OAEs were absent. The absence of OAE responses may occur due to interference from middle ear pathologies even when cochlear function is normal[35]. The other cases that had no OAE did not present changes in the tympanometric curve, which suggests changes in cochlear function and all cases require a complete audiological evaluation to conclude a diagnosis.

Regarding Auditory Evoked Potentials, our data were like those found by Santos et al.[36] and Nogueira et al.[37] in relation to the reduced values of the absolute latency of wave V in the PEATE, which can be justified by a cytotoxic action the Zika virus. Borja et al.[38] carried out hearing screening in microcephalic children exposed to the Zika virus during pregnancy and also observed earlier absolute latencies, suggesting that the neuroconduction of acoustic stimuli in this population may differ from other children, taking into account the affinity of the Zika virus for nervous tissue and cited that the standards available in validated studies may not be applicable to this population.

In a study involving 107 microcephalic children laboratory evidence of congenital ZIKV infection, evaluated the incidence of sensorineural hearing loss during the first three years of life by performing click

PEATE, showing an incidence of 9.3% sensorineural hearing loss[18]. In the present study, the children were only assessed once and late, approximately 77.25 ± 9.5 months after birth, however, the children underwent neonatal hearing screening as determined by multiprofessional committee on auditory health[28]. Although neonatal hearing screening is already a universally accepted method for the early detection of hearing loss, there are false positives and the main causes for failure in OAE tests in newborns are the timing of the test (number of hours of life) and the presence of vernix in the external auditory canal[39]. Of the children who underwent hearing screening, three failed (cases 2,5 and 7). Child 7 passed the retest; however, it is potentially possible that the retest was a false negative and that the child had early hearing loss.

This study has limitations inherent to the study design. Furthermore, although all children were exposed in utero to ZIKV, a causal relationship between microcephaly and hearing loss cannot be established, as IgG to different agents causing TORCH syndrome was evidenced in mothers and children. Furthermore, the children were not monitored over time to identify early or late hearing loss, although they underwent neonatal hearing screening.

## V. Conclusion

In conclusion, we evidenced and described altered electrophysiological and electroacoustic auditory responses in children with microcephaly born during the ZIKV epidemic and exposed in utero to Zika virus and to other potentially agents causing TORCH syndrome. Frequent hearing changes were evidenced, although only a single child had hearing loss, potentially early, confirmed, even in an assessment with more sensitive instruments later. Our results point to the need to evaluate and monitor microcephalic children with audiological assessment instruments throughout their lives, to detect hearing loss and provide appropriate interventions at the appropriate time.

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