LUPINE PUBLISHERS

ISSN: 2641-1709

Scholarly Journal of Otolaryngology

DOI: 10.32474/SJO.2023.09.000320

Review Article

Congenital Zika Syndrome and its Relationship with Hearing Loss in Infants of Hearing in Infants: A Review of the Literature

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Received: February 16, 2023 **Published:** March 14, 2023

Problem Statement

Zika virus is a flavivirus (arthropod-borne virus) transmitted primarily by the bite of an infected Aedes mosquito [1]. During the Zika virus pandemic, more than one million confirmed infected patients were reported in Brazil, which predominated in the north and northeast regions (Pernambuco state and others), declaring a national and international emergency [1] (Zousa EP, 2018). Colombia ranked second among Latin American countries, with more than 47,000 cases [2]. Regarding the repercussions and medical sequelae, two main serious neurological complications related to the virus have been identified: Guillan-Barré syndrome (GBS), and microcephaly, the most serious end of a spectrum of birth defects known as Congenital Syndrome. of Zika (SCZ). According to official reports from the Brazilian Ministry of Health, it is estimated that, between November 2015 and May 2017, more than 6,000 cases of babies with microcephaly were reported, of which 2,722 cases were confirmed and the rest remain under investigation [1]. In Colombia, it is estimated, according to studies published in the pediatric infectious disease journal, that due to the Zika epidemic, nearly 1,000 babies had to be born with microcephaly associated with the virus [2].

Microcephaly is defined by the World Health Organization (WHO) as a head circumference measurement less than or equal to two standard deviations. Below the average for the gestational age and sex of the child at birth. Children with microcephaly secondary to the Zika Virus are grouped under the congenital Zika syndrome (ZICS), the most severe end of a spectrum of birth defects that also include alterations in the sensory functions of vision and hearing, since the Zika virus It is included in the viral infections that cause up to 40% of congenital and acquired hearing losses [2]. The long-term consequences of microcephaly depend on the underly ing brain abnormalities and can range from mild to severe delays in motor development and intellectual deficits, with cerebral palsy and compromised sensory functions such as vision and hearing or hearing loss occurring. (Lowe, Barcellos, Hearing loss can be defined as any disturbance in the normal hearing process, regardless of its cause, type or severity. The limitations of a child with unidentified congenital hearing loss at the beginning of life can lead to alterations in their cognitive, emotional, affective and academic development, as well as in their overall development. The earliest possible identification is justified by the need for immediate intervention, beyond the first 6 months of age.

For the detection of this type of hearing loss, there are electrophysiological triage methods with greater sensitivity and specificity, such as the otoacoustic emission test (OAE) and brainstem auditory evoked potentials (PEATE); A non-invasive examination, which allows the recording of the electrophysiological activity of the auditory system, objectively, (from the auditory nerve to the inferior quadrigeminal tubercle located in the brainstem) described by electrophysiological waves, (I waves being more important, III, V) before a sound stimulus. The PEATE makes it possible to estimate the hearing threshold, characterizing the type and degree of hearing loss, identifying retrocochlear or hearing-related alterations. Central nervous system, also evaluating the maturation of the central auditory system in neonates [3]. In patients with congenital Zika syndrome, brainstem auditory evoked potential (BAEP) testing is more feasible due to the higher prevalence of retrocochlear hearing losses (those characterized by disorders of the auditory nerve that cause information to be processed correctly). through the ear, is not adequately transmitted in the form of electrical impulses to the brain), considering the objectivity and reliability of the instrument in the evaluation of the upper auditory pathway. We

know that, during the development of the via auditory, the answers. Electrophysiological may suffer alterations. Well, according to the literature, only at birth is the distal portion of the cochlear nerve mature (the site where wave I of PEATE is generated), which indicates that the maturation of the auditory pathways involves different mechanisms in the central areas. and peripheral, because nerve impulse conduction depends on changes in speed associated with myelination and changes in synaptic efficiency of the nuclei of the auditory pathway [2,4]. In this sense, the auditory responses (with PEATE) of neonates and infants are influenced by the maturational process of the auditory system, whose responses may be affected by exposure to certain viruses such as Zika causing hearing difficulties.

Given the above, and knowing at a general level the possible repercussions and sequelae of the Zika virus on the hearing of infants, this research aimed to argue in a strict sense the relationship between the congenital Zika syndrome and hearing loss in children through of an argumentative type methodology based on a brief review of the existing literature. After carrying out the search, selection and cleaning methodology of articles that met or did not meet the inclusion criteria for the study, that is, those that addressed all or some of the variables that were the object of our study, those that responded directly or hint to the central research question: is there a relationship between Zika Congenital Syndrome and hearing loss in children? In this order, the scientific articles that argue our thesis are developed.

Development

The Zika virus was isolated for the first time in 1947 and in 1952 antibodies against it were identified in humans, sporadic reports being reported in different parts of the world, the most important in recent history being those detected in Micronesia in 2007 and in Polynesia in 2013. Zika virus disease is an infection that is grouped into the category of acute exanthematic diseases transmitted by arthropods similar to those that cause dengue, chikungunya, and yellow fever. The main symptoms include fever, rash, muscle aches, headache, among others. Zika is not a new virus, according to reports. The literature circulated in the continents of Asia and Africa more than half a century ago. But it was not until 2015 when it had its highest spread peak in the northwestern regions of Brazil, in which the spread centers and the ministries of health issued the alert and identified an unknown rash disease in the provinces of Pernambuco, Rio Grande del Sur and Bahia, whose spread has spread to more than 31 countries in the region, involving all age groups and with apparently mild manifestations [1].

Zika virus disease depends on the distribution of the primary vector, the Aedes aegypti mosquito, and a secondary vector, Aedes albopictus. Transmission of Zika infection is possible not only in countries of the southern hemisphere, but also in those of the northern hemisphere such as the United States from human primates. The main vectors from which the Zika virus is released are the Aedes africanus, Aedes luteocephalus, Aedes aegypti, Aedes albopictus mosquitoes, the aegypty strain predominating in the Latin American regions causing more than one million of confirmed infected patients in Brazil, [5] and more than 47.00 cases in Colombia, ranking second among Latin American countries in terms of affectations by this virus [2]. Virus transmission occurs both in urban and suburban areas in larval habitats such as natural and artificial containers closely related to peridomestic environments. The Zika vector is a daytime, highly anthropophilic and endophilic blood-consuming mosquito, making its power to infect people more likely. However, its potential vector lies not only in its bite but also in the hands of destructive processes for humans but favorable for mosquito reproduction, such as the climate, the underlying conditions of housing and community environments, the temperature, among others. . According to Brazilian health authorities, this rapid spread of the virus in the northern areas was due to the combination of these factors such as a susceptible population exposed, climatic conditions that favor the propagation of the vector (humid climates and hot lands, coasts), dynamic non-vector transmission, and the constant mobility of these populations. It is for them that the regions most affected by this epidemic were those located in the northern areas with the highest population density, with tropical climates such as Pernambuco, Bahia State and Rio Grande do Sul, leaving almost. Except for this, the most remote populations in the south whose climatic conditions did not favor the propagation of the vector [1]. Zika was considered a disease of low prevalence and acuity until the sudden appearance of newborns with microcephaly, in which maternity services began to report a sharp increase in children with a prenatal history of Zika infection in their mothers with this condition. It is from there that the public health emergency is declared, considering an association of microcephaly as a consequence of the gestational disease of the mothers.

Regarding the repercussions and medical sequelae, two main serious neurological complications related to the virus have been identified: Guillan-Barré syndrome (GBS), and microcephaly, the most serious end of a spectrum of birth defects known as Congenital Syndrome. of Zika (SCZ), the main object of development in our theme. Guillain Barre Syndrome (GBS) is an idiopathic acute inflammatory demyelinating polyneuropathy of autoimmune etiology, characterized by muscle weakness and areflexia. It is presumed that an infectious organism induces the immune response (generally HIV, dengue, influenza) and less frequently by vaccination, although in recent years there has been an increase in incidence, which is attributed to the Zika virus (ZIKV) and chikungunya. If the patient is not treated promptly, he can develop various complications, which lead to prostration and even death. Its incidence is between 1 and 3 cases per 10,000 inhabitants per year, of which there is a tendency towards males and affects all age groups regardless of age (Benavides-Melo et al.). According to official reports from the Brazilian Ministry of Health, it is estimated that, between November 2015 and May 2017, more than 6,000 cases of babies with microcephaly, of which 2,722 cases were confirmed and the rest remain under investigation [1]. In Colombia, it is estimated, according to studies published in the pediatric infectious disease journal, that

due to the Zika epidemic, close to 1000 babies with microcephaly associated with the virus had to be born [2].

a) Microcephaly: It is defined by the World Health Organization (WHO) as a head circumference measurement less than or equal to two standard deviations below the mean for the gestational age and sex of the child at birth. Children with microcephaly secondary to the Zika Virus are grouped under the Zika congenital syndrome (ZCS), which comprises a set of anomalies associated with the prenatal period related to intracanal calcifications, and other malformations of the head and eyes, mainly neurological disorders. posterior fossa, cortical or subcortical cerebral atrophy and asymmetry, hydranencephaly, ventriculomegaly, impaired neural migration, cerebral calcifications, abnormally formed brain structures such as the corpus callosum, thalamus, pons, cerebellar vermis.

Although this is a virus that is part of the category of exanthematic diseases, infections by other viruses such as West Nile or dengue do not yet seem to significantly increase the risk of congenital anomalies. Mother-to-child transmission of other infections does not related as rubella or cytomegalovirus, lymphocytic choriomeningitis, while there has been more literature and evidence that Toxoplasmosis has been associated with microcephaly, as well as other presentations of these congenital infections include brain alterations calcinations, hydrocephalus ocular alterations such as cataracts, chorioretinitis, hearing damage, head size at birth, reduced brain growth with a high risk of long-term adverse alterations including auditory visual intellectual alterations and seizures [6]. It is very important to also take into account that this spectrum of congenital microcephaly can be associated with prenatal exposure to other infectious and non-infectious agents such as alcohol, metabolic problems or disorders, therefore these etiologies have to be fully evaluated when infection by the congenital microcephaly occurs. Zika virus has been excluded as a differential diagnosis.

As for the description of other alterations, the spectrum of congenital Zika syndrome (CZS) also includes alterations in hearing functions, since the Zika virus is included in the viral infections that cause up to 40% of hearing losses. congenital and acquired hearing [7]. In general, hearing loss caused by viruses is usually of the congenital or late retrocochlear type, those that affect the auditory nerve behind the inner ear, hindering the electrical transmission of auditory information captured by the ear [8]. The ear works as a signal transducer that captures a disturbance in the environment, propagates it, modifies it, and transforms it into an electrical signal to send it to the brain, which processes it, interprets it, and gives it meaning. It is made up of three fundamental parts, the external ear, the middle ear and the internal ear [9]. The external ear is composed of the auricle, a sheet of cartilage folded in various irregular directions supported by ligaments and skin. Among its functions is the protection of the external auditory canal to prevent the entry of foreign or infectious bodies, as well as the hearing function, in which it collects the sound signals and directs them into the external auditory canal (EAC). The EAC is the other portion that constitutes the external ear originating from the base of the auricle and extends to the eardrum. The external auditory system is made up of skin and cartilage, just as the auricle exerts a protective function by containing an irregular shape, cilia inside, and the secretion of substances that prevent foreign bodies from entering the ear. Likewise, it has the function of conducting the sound waves that are directed by the auricular pavilion which exert a dynamic resonance of the frequencies between 2,000 and 5,000 hz.

a. Middle ear: composed of the tympanic cavity, the mastoid cells and the Eustachian tube. It is considered an impedance adapter between the air medium and the liquid medium, conversion of vibrations into acoustic waves, protection of the inner ear against high-impact sound stimuli and pressure maintenance.

b. Inner ear: It is made up of a series of cavities excavated in the temporal bone, the osseous labyrinth, which in turn contains the membranous labyrinth, which houses two sensory receptors: the auditory receptor (cochlea) and the balance receptor (vestibule). Among its functions are those of electrical transmission and tonotopic activity that arises from the stimulation of the external hair cells by stimulating the portions of the cochlea and with it the low, medium and high frequencies. Likewise, the production of an electrical impulse that is conducted through the afferent pathways or eighth cranial nerve to the cerebral cortex (Manrique & Marco, 2014). Among the studies necessary to evaluate the ear or hearing, there are those basic tests such as otoscopy, which evaluates the structure of the external ear and part of the middle ear, impedance testing that evaluates the middle ear, external auditory canal, audiometry, which is the Gold Standard test for assessment audiological. Is a subjective test whose function is to determine air-bone thresholds and classify them according to normality or abnormality and logo audiometry, this test is the one that measures hearing performance in relation to language.

These tests have some prerequisites for their praxis, within which age, state of health, anatomy and other factors must be taken into account for their analysis and application. In our study, because we are dealing with infants exposed to anatomical alterations, with underlying problems of brain injury, convulsive syndromes, and severe intellectual deficits [1], the application of the basic package as an object variable was not appropriate, therefore, we concentrated on those studies that derive objective tests, which do not require the direct collaboration of the user, obtaining greater reliability and specificity in them. Within the objective complementary tests of the study of hearing in its electrical activity we have the range of auditory evoked potentials of the brain stem (BAEP). These tests evaluate the conduction of the electrical stimulus from the cochlea to the cerebral cortex, measuring the latencies in different portions of the path (spiral ganglion, cochlear nuclei, superior olivary complex, quadrigeminal follicle, geniculate ganglion) of waves I, II, III, IV, V. It is a non-invasive and highly reliable test. The follow-up of infants with congenital Zika infection will depend on the affectation found, and different specialists must coordinate during the first month of life, as well as subsequent evaluation during the first year of vision, hearing, feeding, growth, neurological and endocrine function.

Family members and caregivers will need psychosocial support and assistance in coordinating care [10].

The only way to prevent possible congenital Zika virus infection is to prevent infection in the mother. Women who are pregnant or planning a pregnancy should consider the need to travel to areas where there is Zika virus transmission and avoid it if it is not essential [10]. The long-term consequences of microcephaly depend on the underlying brain abnormalities, and can range from mild to severe delays in motor development and intellectual deficits, cerebral palsy and compromised sensory functions such as hearing (hearing loss), assessed with PEATC [1,2] as shown below through research called Hearing Loss in Infants with Microcephaly and Evidence of Congenital Zika Virus Infection carried out at the Agamenon Magalhães hospital, in the state of Pernambuco, (Brazil), between 2015 and 2016, a possible relationship between the Zika virus and the loss of hearing in infants. In this work, 69 children with congenital Zika syndrome were evaluated, of which 7 presented hearing loss [11]. The tests were distributed in two moments, evidencing that in the first evaluation more than 22% of those evaluated did not pass the detection test in at least one ear, 8 failed the repetition test, which were reassessed by specific frequency potentials, confirming conductive hearing impairment in 2 neonates and 5 neurosensory type, a percentage that was corroborates the epidemiology of other viruses [6].

Along the same lines, Carvalho A, et al. [12] characterized the neurophysiological and neuroimaging clinical findings in children with Zika virus-related microcephaly, concluding that the 102 evaluated infants exposed to Zika at gestational age had a high frequency of brain abnormalities. Most of them had severe neurological findings, frequent epileptiform activity and signs suggesting neurosensory alterations, reporting hearing loss in 17%. Subsequent studies, such as that of Leal M, Ferreira M, et al. provided the case of a newborn also with microcephaly, of twin gestation, evaluated with STEP with Click stimulus, and specific frequency STEP with toneburst stimulus, whose click STEP indicated absence of responses bilaterally and specific frequency STEP with Toneburst stimulus confirmed absence of bilateral responses and bilateral hearing loss with the presence of responses of only 99 dBNA at 2000HZ in the right ear, confirming the relationship of the variables. However, the study called characterization of brainstem auditory evoked potential (AEP) in newborns infected with zika virus [7], whose object of study was to characterize the audiological findings of newborns with evoked potentials brainstem auditory tests in 20 neonates infected with Zika virus during the first 6 months of age, concluded that Zika virus infection, although it did not significantly alter the electrophysiological thresholds of the sample, did show variations in the characteristics of the electrophysiological waves. which showed alterations mainly in the latencies of waves III and V with respect to the initial results and the secondary evaluation (at 6 months). As we can see, hearing loss is present in the various populations of infants evaluated through objective tests, which allow obtain important responses of the electrical activity at the level of the nerve and the auditory pathway, presenting notable failures in children with congenital Zika syndrome.

These hearing alterations in which not only absent responses of the nervous pathway and cochlea functions are evidenced [11], demonstrate the commitment of the Syndrome spectrum in electrophysiological activity and even conductive hearing, findings compatible with other viruses that are part of the same category as Zika. Hearing loss associated with other congenital viral infections is well described and is a well-established feature of other congenital infections, such as cytomegalovirus, rubella, toxoplasmosis, herpes simplex, and syphilis [8]. In these syndromes, the hearing loss is sensorineural, usually bilateral, and severe or profound; it is often undetectable at birth, and sometimes it is progressive or fluctuating. Findings that are correlated in most of the studies, in which neurosensory affectation of the auditory pathway was determined through the evaluation with BAEP [11], being able to locate certain damages or lesions in the areas that drive the nervous stimulus to the brain, in the superior olivary complex, the cochlear nuclei, among others. This information is useful and is corroborated by imaging studies performed in the gestational stages of fetuses with a history of Zika virus, in which a wide spread of lesions at the brain level is observed, such as cerebral or subcortical atrophy and asymmetry, hydranencephaly, calcifications and migration disorders neural, and brain stem. Regarding the degree and type of hearing loss, this aspect is evidenced in the studies found in which, mainly, profound neurosensory or retrocochlear losses predominate [11], those that are characterized by affections of the auditory nerve, which mean that the information correctly processed by the ear is not adequately transmitted in the form of electrical impulses to the brain, a situation that demonstrates that the damage to the structure of the auditory system is localized from the cochlea or the initiation of electrical activity as occurs with other viruses. However, the central origin of the problem cannot be ruled out. Since, studies already carried out on the power of toxicity showed that the virus acts by killing the cells that give rise to neurons, thus impairing neuronal communication, causing a diminished cortex and, even hypoplasia at the level of the brainstem, being able to cause progressive (acquired) hearing loss [2].

Undoubtedly, the spectrum of hearing impairments is very varied, as described by neuroimaging studies [12], the virus causes complex bone malformations that include a set of associated anomalies such as intracaneal calcifications, and other malformations of the head and eyes, neurological alterations mainly of the posterior fossa, cortical or subcortical cerebral atrophy and asymmetry, hydranencephaly, ventriculomegaly, neural migration disorders, cerebral calcifications, abnormally formed cerebral structures such as the corpus callosum, the thalamus, the pons, the cerebellar vermis, among others (Torres, 2017), anomalies that affect the development of brain areas, causing epileptiform activity, since it prevents their growth,its evolution and the establishment of functions, such

as hearing. On the other hand, it is necessary to infer that the association between SCZ and hearing loss is not absolute, since studies such as Rodrigues, P & colbs [7] report that there was no statistically significant association between these two variables, that is, hearing loss secondary to Zika in those children with a prenatal history of Zika the infection. But, however, the variations in the electrophysiological activity were evident in the two moments of the evaluation. Results that other researchers attribute to the immaturity of the upper auditory pathway because, during the development of the auditory pathway, the electrophysiological responses may suffer alterations.

In this sense, the absence of latencies in the waves evaluated is not a reliable result in terms of physiological maturation of the pathway, since, according to authors, at birth only the distal portion of the cochlear nerve is mature (site where PEATE wave I is generated), which indicates that the maturation of the auditory pathways involves different mechanisms in the central and peripheral areas, because nerve impulse conduction depends on changes in speed associated with myelination and changes in efficiency synaptic nuclei of the auditory pathway [2,4]. In this sense. In this regard, other authors complement by referring to steady-state auditory responses (WEEE), which increase in the first weeks of life, and may subsequently suffer alterations such as a decrease in the amplitude when passing the stimulus, and greater intensity (EEG) in the internal noise. The foregoing is corroborated with the postulates of the literature referring to the changes suffered by the results of PEATE waves in neonates and infants, as well as in the infant stage (before 5 years of age), due to the permanence and power of destruction (toxicity) of Zika virus in brain cells (CNS) [13-22].

Conclusion

According to the studies reviewed in our research, there is little scientific evidence that can provide us with a significant and absolute association between congenital Zika syndrome and hearing loss in infants. However, the few studies that currently exist provide us with solid bases to establish relative conclusions about the relationship between both variables. Zika has generated disturbances in the normal hearing process of the children involved since pregnancy, and regardless of its cause, type or severity, the limitations of these children with unidentified congenital hearing loss at the beginning of life, can lead to alterations in their cognitive, emotional, affective and academic development, as well as in their global development. The earliest possible identification. The Zika virus has passed, but its consequences in the medium and long term will persist in the hearing of those children who were affected by this virus, demanding great challenges for the health professionals in charge of the care and rehabilitation of hearing impairment. In this sense, it is essential to feed the existing literature with more research that allows to fully quantify the existing cases to date in order to provide the system with important bases to initiate public policies in favor of the rehabilitation of this population. Zika has constituted a threat for the affected countries, but also an opportunity in terms of research and therapeutic options, those focused on enabling the auditory sensor, such as cochlear implants and implantable methods for hearing rehabilitation. Undoubtedly, the Zika virus has jeopardized the health systems of Brazil and Colombia, its consequences not only require the attention of the health system, but also those systems that allow a comprehensive rehabilitation of the child and their families in social, economic and educational aspects. Therefore, it is necessary to characterize in a broader way the physical sequelae and social consequences derived from this epidemic, implement more and better case tracking systems, greater follow-up and monitoring of disabled children with priority access to health, education and economic benefits.

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