Seizure: European Journal of Epilepsy 103 (2022) 92–98

Contents lists available at ScienceDirect

Seizure: European Journal of Epilepsy

journal homepage: www.elsevier.com/locate/seizure

Characteristics associated with drug resistant epilepsy in children up to 36 months old with Congenital Zika Syndrome

Tamires Barradas Cavalcante [a], Marizélia Rodrigues Costa Ribeiro [b], Patrícia da Silva Sousa [c], Elaine de Paula Fiod Costa [d], Maria Teresa Seabra Soares de Britto e Alves [a], Vanda Maria Ferreira Simões [a], Rosângela Fernandes Lucena Batista [a], Eliana Harumi Morioka Takahasi [a], Gláucio Andrade Amaral [e], Ricardo Khouri [f], Maria dos Remédios Freitas Carvalho Branco [a], Ana Karolina Torres Mendes [a], Luciana Cavalcante Costa [a], Marcos Adriano Garcia Campos [a], Antônio Augusto Moura da Silva [a,*]

[a] Department of Public Health, Programa de Pós-Graduação em Saúde Coletiva, Federal University of Maranhão, Rua Barão de Itapary, 155, Centro, São Luís, Maranhão 65020- 070, Brazil
[b] Department of Medicine III. Federal University of Maranhão, São Luís, Maranhão, Brazil
[c] Reference Center on Neurodevelopment, Assistance and Rehabilitation of Children/NINAR – Health Secretariat of the State of Maranhão. São Luís, Maranhão, Brazil
[d] Department of Medicine I, Federal University of Maranhão, São Luís, Maranhão, Brazil
[e] Sarah Network of Neurorehabilitation Hospitals, São Luís, Maranhão, Brazil
[f] Laboratory of Vector-Borne Infectious Diseases, and Department of Pathology and Legal Medicine, Gonçalo Moniz Institute, Fiocruz-Bahia, Faculty of Medicine, Federal University of Bahia, Salvador, Bahia, Brazil

ARTICLE INFO

Keywords:
Zika virus
Microcephaly
Epilepsy

ABSTRACT

Objectives: To verify characteristics associated with drug resistant epilepsy in children up to 36 months of age with Congenital Zika Syndrome (CZS).
Methods: This is a prospective cohort study with children aged up to 36 months diagnosed with CZS. Obstetric, demographic, phenotype and other clinical signs, cranial tomography, growth and motor development of the children were collected.
Results: Of a total of 109 children diagnosed with CZS, 100 (91.7%) had epilepsy and 68 (68%) with drug resistant seizures. The types of seizures associated with drug resistant epilepsy were focal seizures from the occipital lobe, generalized tonic and generalized tonic-clonic seizures. There was an association between drug resistant epilepsy and microcephaly at birth, severe microcephaly at birth, excess nuchal skin, ventriculomegaly, reduced brain parenchyma volume, and hypoplasia or malformation of the cerebellum. Difficulty sleeping, irritability, continuous crying, dysphagia and gross motor function were clinical signs associated with drug resistant epilepsy, as were the presence of ocular abnormalities, low head circumference in the first year of life and low weight in the first six months.
Conclusions: The prevalence of drug resistant epilepsy in children up to 36 months with CZS was 62.4% and was associated with the severity of the child's neurological damage, with emphasis on the reduction of brain parenchyma volume and damage to the cerebellum.

1. Introduction

In November 2015, the Brazilian Ministry of Health declared the Zika virus (ZIKV) outbreak a public health emergency following an increase in microcephaly cases, especially in northeastern Brazil [1]. Since the beginning of reports of children with Congenital Zika Syndrome (CZS), epileptic seizures are the main clinical complication in the first 4 months of life [2]; they tend to be early [3,4] and refractory [4].

In CZS, epileptic seizures are the main cause of hospitalization and demand for emergency services [2] and are more common than in

* Corresponding author.
E-mail address: aamouradasilva@gmail.com (A.A.M. da Silva).

https://doi.org/10.1016/j.seizure.2022.11.001
Received 20 June 2022; Received in revised form 22 October 2022; Accepted 3 November 2022
Available online 4 November 2022

congenital infections caused by STORCH pathogens (syphilis, toxoplasmosis, rubella, cytomegalovirus and herpes simplex). The development, with constant and intense lack of control of the epileptic condition, is one of the causes of concern, fear and anguish of families of children with CZS [5].

In drug resistant epilepsy, the mechanisms of drug resistance are likely to be variable and multifactorial [6]. In CZS, the response to anti-seizure medication (ASM) is extremely low, ranging from 20% in the first year to 30% in the second year of life, and is associated with extensive neurological damage caused by ZIKV in the cortical structures of patients [7]. Studies with previous clinical and neurological evaluation in children with CZS who have epilepsy, especially up to three years of age, are necessary for a better understanding of resistance to ASM [8].

Patients with drug resistant epilepsy have increased risks of death, injuries, psychosocial dysfunction and reduced quality of life [9] In this sense, active screening and treatment for children with CZS who have epilepsy are important [2]. Knowledge about factors associated with drug resistant epilepsy in children with CZS is essential for prognosis. This study verifies the association between obstetric data, demographic characteristics, clinical signs, phenotype, growth, motor development and cranial tomography with drug resistant epilepsy in children with CZS.

2. Methods

This is a prospective cohort study of children with CZS born in maternity hospitals in the state of Maranhão, Brazil, from March 2015 to September 2018, followed up at a referral center for neurodevelopment, assistance and rehabilitation of children (NINAR).

We included children up to 36 months of age, diagnosed with CZS and with data on the presence and/or treatment of epilepsy. Children were followed up for an average of every three months, being able to verify their exposure to therapeutic changes and clinical evolution of their epileptic seizures. For growth analyses, children with hypertensive hydrocephalus were excluded because Head Circumference (HC) and weight values tend to be higher due to this condition.

We consider drug resistant epilepsy, also called refractory epilepsy, when two or more protocols of ASM, used alone or in combination, have failed to control seizures in a sustained way – International League Against Epilepsy (ILAE) classification system [9].

Characteristics of epileptic seizures (age of onset, seizure types, and ASM) were collected and analyzed by a pediatric neurologist. Obstetric, demographic and birth data were obtained retrospectively from medical records and from the Child's Health Handbook. Other clinical data such as the presence of spasticity, difficulty sleeping, irritability, dysphagia and continuous crying were extracted from the medical records. The diagnosis of CZS in this cohort [10–12] occurred through classification into 4 categories: (a) confirmed by plaque reduction neutralization test (PRNT 90)>1:10, (b) Probable laboratory case, with positive enzyme immunosorbent assay for immunoglobulin M when PRNT was negative or not performed, (c) highly probable clinical case with lesions on computed tomography (CT) of the brain suggestive of CZS and negative results for STORCH (syphilis, toxoplasmosis, rubella, cytomegalovirus and herpes simplex), (d) moderately likely clinical case with brain CT lesion suggestive of CZS and incomplete or inconclusive results for STORCH [10]. All children had phenotype and CT findings suggestive of CZS. PRNT collection occurred at a mean age of 22 months, with a standard deviation of six months of age [11].

Obstetric data were type of delivery (normal and cesarean) and gestational trimester of onset of maternal symptoms of ZIKV virus infection during pregnancy (first, second, and third). We considered symptoms present when the mother reported a rash or two of the following symptoms: fever, pruritus, arthralgia/joint swelling, conjunctivitis, and headache, dichotomized into yes and no. Regarding the child, sex was the demographic data collected. Low birth weight was defined as birth weight <2500 g and preterm birth as <37 completed weeks of gestational age. Phenotype data, such as frontotemporal retraction, craniofacial disproportion, prominent occipital, biparietal depression, excess nuchal skin, and the signs of fetal akinesia deformation sequence - arthrogryposis and congenital clubfoot [13] were also recorded.

Computed tomography (CT) scans of the skull were performed in children up to two years of age and were analyzed by two neuroimaging specialists who were unaware of the laboratory findings. The following changes characteristic of CZS were investigated: calcifications, reduced brain parenchyma volume, ventriculomegaly, malformation of cortical development, malformation/hypoplasia of the cerebellum, malformation/hypoplasia of the brainstem, and agenesis/dysgenesis of the corpus callosum.

A trained physical therapist assessed the degree of motor impairment for children according to gross motor function – classification system (GMFCS) [14] validated for Portuguese in Brazil [15] at five levels: I – walks without limitations; II – walks with limitations; III – walks using a manual mobility device; IV - self-mobility with limitations. Can use motorized mobility; V – transported in a manual wheelchair.

An ophthalmologist performed an eye examination by biomicroscopy and indirect ophthalmoscopy. Findings were documented with wide-angle fundus photography using the RetCam Shuttle System (Clarity Medical Systems, Pleasanton, CA, USA). The following ophthalmic lesions were examined: chorioretinal scar, mobilization of retinal pigment, optic nerve pallor, optic nerve hypoplasia, bilateral retinal change, and bilateral optic nerve change.

HC, weight, weight for length and length at birth were extracted from medical records and at 6, 12, 24 and 36 months were collected by trained personnel following a standardized protocol. The HC was measured with an extensible tape, passed around the head, anchored above the eyebrows and over the children's occiput. The INTERGROWTH-21st online program [16] was used to calculate Z-scores for HC, weight and length according to sex and gestational age at birth, with gestational age corrected for preterm children. We used the criteria of the World Health Organization (WHO) [17,18] to classify microcephaly, weight, weight for height, and height after birth, which was considered when the Z score was >2 standard deviations (SD) below the average for sex and age. We considered severe microcephaly as a HC Z-score >3 SD below the mean for sex and age [16].

Data were stored in RedCap software and analyzed in STATA® 14.0. Data description was performed using frequencies and percentages. The normality of numerical variables was evaluated based on symmetry and kurtosis. Pearson's chi-square and Fisher's exact tests were used to verify associations between the categorical variables and the T test for independent samples and Mann Whitney's test to compare the mean Z-scores, according to the normality of the distribution between the groups with and without drug resistant epilepsy.

This study was approved by the Research Ethics Committee of the University Hospital of the Federal University of Maranhão, Brazil, certificate of presentation of ethical assessment number 65,897,317.1.0000.5086. and protocol number 1,510,315.

3. Results

Of a total of 110 children diagnosed with CZS, 109 had information about the presence or absence of epilepsy in their medical records. Of these, 9 (8.3%) had no epileptic seizures and 100 (91.7%) had epilepsy within the first 36 months of life. A total of 68 (62.4%) children had drug resistant epilepsy (Table 1).

We did not find an association between age at first epileptic seizures and the presence of drug resistant epilepsy ($p = 0.055$). Among the occurrence of each type of epileptic seizure, those that were associated with drug resistant epilepsy were focal seizures from the occipital lobe based on electroencephalogram (EEG)/video EEG and clinical data ($p < 0.001$), generalized tonic ($p = 0.040$) and generalized tonic-clonic ($p = 0.008$). Almost all types of seizures had association with drug resistant

Table 1
Clinical characteristics of epilepsy and presence of drug resistant epilepsy in children with congenital Zika syndrome. São Luís, 2016–2018.

Characteristics	Drug resistant epilepsy (n = 109)[a]				P-value
	Yes		No		
	No.	(%)	No.	(%)	
Epileptic seizures (n = 109)					
No	0	0.0	9	100.0	
Yes	68	68.0	32	32.0	
Age at first epileptic seizures (n = 98)					0.055[b]
<6 months	43	75.4	14	24.6	
6 to 11 months	17	68.0	8	32.0	
>=12 months	7	43.7	9	56.3	
Focal seizures from the frontal lobe (n = 98)					0.055[b]
No	20	52.6	18	47.4	
Yes	43	71.7	17	28.3	
Focal seizures from the occipital lobe (n = 97)					<0.001[c]
No	5	21.7	18	78.3	
Yes	58	78.4	16	21.6	
Generalized epileptic spasms (n = 105)					0.665[c]
No	3	4.5	3	7.9	
Yes	64	95.5	35	92.1	
Generalized tonic seizures (n = 97)					0.040[b]
No	27	55.1	22	44.9	
Yes	36	75.0	12	25.0	
Generalized tonic-clonic seizures (n = 97)					0.008[c]
No	45	58.4	32	41.6	
Yes	18	90.0	2	10.0	
Number of anti-seizure medications used (109)					
0 or 1	0	0	25	61.0	
2 to 4	45	66.2	16	39.0	
above 4	23	33.8	0	0	

[a] 109 children with Congenital Zika Syndrome with known data on epilepsy.
[b] Chi-square test.
[c] Fisher's exact test.

epilepsy (Table 1).

The ASM most frequently used by children with drug resistant epilepsy were vigabatrin (69.1%), cannabidiol (66.2%), topiramate (63.2%), phenobarbital (50.0%), valproate (45.6%) and levetiracetam (44.1%). Among children who did not have drug resistant epilepsy, topiramate (29.3%) was the most used medication. Of the children with drug resistant epilepsy, 66.2% used 2 to 4 ASM in their first 36 months of life.

Of the 83 mothers with symptoms of Zika virus infection during pregnancy, 55 (66.2%) had symptoms in the first semester of pregnancy. Drug resistant epilepsy was not associated with maternal infection trimester ($p = 0.173$), type of delivery ($p = 0.130$), sex ($p = 0.439$), low birth weight ($p = 0.876$), preterm birth ($p = 0.926$) or PRNT ($p = 0.279$) (Table 2).

Regarding the CZS phenotype, of the 109 children studied, 92 (84.4%) had a known HC at birth. There was an association between drug resistant epilepsy and microcephaly (HC Z score< 2SD) at birth ($p = 0.038$), severe microcephaly (HC Z score< 3SD) at birth ($p = 0.023$), and excess nuchal skin ($p = 0.011$). In addition, 70.5% of children with microcephaly at birth, 75% with severe microcephaly at birth and 84.6% with excess nuchal skin had drug resistant epilepsy. Features of fetal akinesia syndrome, such as arthrogryposis ($p = 0.318$) and congenital clubfoot ($p = 0.253$) were not associated with drug resistant epilepsy (Table 3).

Among the clinical characteristics, an association was observed between drug resistant epilepsy and difficulty sleeping ($p = 0.005$), irritability ($p = 0.007$), dysphagia ($p < 0.001$), continuous crying ($p = 0.002$), and transported in a manual wheelchair (GMFCS level V) ($p = 0.035$), with a higher percentage of drug resistant epilepsy when these clinical findings were also present. No association was found between

Table 2
Clinical, demographic and laboratory characteristics and presence of drug resistant epilepsy in children with congenital Zika syndrome. São Luís, 2016–2018.

Characteristics	Drug resistant epilepsy (n = 109)[a]				P-value
	Yes		No		
	No.	(%)	No.	(%)	
Trimester of maternal infection during pregnancy (n = 83)[b]					0.173[d]
First	36	65.4	19	34.6	
Second	13	68.4	6	31.6	
Third	3	33.3	6	66.7	
Type of delivery (n = 109)					0.130[c]
Vaginal	28	54.9	23	45.1	
Cesarean	40	69.0	18	31.0	
Sex (n = 109)					0.439[c]
Male	38	59.4	26	40.6	
Female	30	66.7	15	33.3	
Low birth weight (n = 106)					0.876[c]
No	52	62.6	31	37.4	
Yes	14	60.9	9	39.1	
Preterm birth (n = 104)					0.926[c]
No	58	64.4	32	35.6	
Yes	8	57.1	6	42.9	
PRNT (n = 93)[e]					0.279[c]
Negative	35	66.0	18	34.0	
Positive	22	55.0	18	45.0	

[a] 109 children with Congenital Zika Syndrome with known data on epilepsy.
[b] 23 asymptomatic mothers and 3 others who did not know whether they had symptoms attributable to ZIKV infection during pregnancy were excluded.
[c] Chi-square test.
[d] Fisher's exact test.
[e] PRNT – Plaque Reduction Neutralization Test.

drug resistant epilepsy and spasticity ($p = 0.553$) (Table 4).

Among the CT findings, there was an association between drug resistant epilepsy and ventriculomegaly ($p = 0.027$), reduced cerebral parenchyma ($p = 0.036$), hypoplasia or malformation of the cerebellum ($p = 0.022$); when present, these findings imply a higher percentage of children with drug resistant epilepsy (Table 5).

The presence of any ophthalmic lesion was associated with the presence of drug resistant epilepsy ($p = 0.004$) as well as, separately, the chorioretinal scar ($p = 0.002$), with 90.9% of the affected children also presenting drug resistant epilepsy. The other ophthalmic damages analyzed separately were not associated with drug resistant epilepsy (Table 6).

For the growth analyses, of the 109 children with CZS and known epilepsy data, we excluded 2 (two) because they had hypertensive hydrocephalus at birth. It is possible to observe that the differences in HC Z-score between the groups with and without drug resistant epilepsy decrease over time and cease to be significant after 24 months. Regarding the other growth data, only weight for age at six months ($p = 0.044$) and at 36 months ($p = 0.042$) showed a difference between the groups with and without drug resistant epilepsy (Table 7), being lower in the group presenting drug resistant epilepsy.

4. Discussion

The prevalence of drug resistant epilepsy in children up to 36 months with CZS was 62%. Drug resistant epilepsy was associated with the presence of ventriculomegaly, reduced cerebral parenchyma and hypoplasia or malformation of the cerebellum. It was also associated with other clinical variables commonly associated with epilepsy – irritability, continuous crying, difficulty sleeping and dysphagia. The most common seizures in children with drug resistant epilepsy were focal seizures from the occipital lobe, generalized tonic and generalized tonic-clonic.

We suggest that association of drug resistant epilepsy and neurodevelopment occurs in the more severe cases and are consequences of

Table 3
Phenotype characteristics of fetal brain rupture sequence and presence of drug resistant epilepsy in children with Congenital Zika Syndrome (n = 109). São Luís, 2016–2018.

	Drug resistant epilepsy (n = 109)[a]				P-value
	Yes		No		
	No.	(%)	No.	(%)	
Microcephaly at birth (n = 92)[b]					0.038[c]
No	15	48.4	16	51.6	
Yes	43	70.5	18	29.5	
Severe microcephaly at birth (n = 92)[b]					0.023[c]
No	25	52.1	23	47.9	
Yes	33	75.0	11	25.0	
Frontotemporal retraction (n = 107)					0.846[c]
No	18	62.1	11	37.9	
Yes	50	64.1	28	35.9	
Craniofacial disproportion (n = 107)					0.708[d]
No	6	75.0	2	25.0	
Yes	62	62.6	37	37.4	
Occipital protuberance (n = 107)					0.246[c]
No	27	57.5	20	42.5	
Yes	41	68.3	19	31.7	
Biparietal depression (n = 107)					0.089[c]
No	32	56.1	25	43.9	
Yes	36	72.0	14	28.0	
Excessive nuchal skin (n = 107)					0.011[d]
No	46	56.8	35	43.2	
Yes	22	84.6	4	15.4	
Arthrogryposis (n = 106)					0.318[d]
No	59	61.5	37	38.5	
Yes	8	80.0	2	20.0	
Clubfoot (n = 106)					0.253[d]
No	60	61.2	38	38.8	
Yes	7	87.5	1	12.5	

[a] 109 children with Congenital Zika Syndrome with known data on epilepsy.
[b] 15 children with no known head circumference at birth and 1 (one) with hypertensive hydrocephalus at birth were excluded.
[c] Chi-square test.
[d] Fisher's exact test.

the cerebral damage. It is also possible that clinical characteristics associated with drug resistant epilepsy influenced growth and, mainly, the neurodevelopment of these children.

We believe that the follow-up time of 36 months in this cohort contributed to the entry of epilepsy cases with onset after 12 months of age, which is one of the strengths of this study. The prevalence of epilepsy and drug resistant epilepsy in this age group contributes to write the disease history. The cohort of 109 children is one of the largest on the subject, and the longer follow-up time makes it possible to verify the association between drug resistant epilepsy with other characteristics of the children and infer clinical severity.

The study has some limitations. The convenience sample attended at a referral center can bring bias to the study, due to the greater severity of children whose family sought the health service. It may have been difficult for family members to recognize and report the types of seizures in children, especially mild ones. Economic and personal factors may have influenced family members' adherence to the medication protocol prescribed for the child.

The percentage of children in this cohort who had epilepsy was 91.7%, which is considered high when compared to other cohorts [5, 19]. In a systematic review with meta-analysis on epilepsy in children with CZS, when analyzing 14 studies on the topic, the percentage of children with CZS and epilepsy was 60%, with higher percentages in studies with older children [7]. In the present study, most children had the onset of seizures in the first six months of life, and of these, 70.2% were drug resistant.

CZS is associated with a high risk of developing epilepsy in the first few years of life [19]. In the study by Van der Linden, of the 141 children analyzed up to 9 months of age, the 95 children who had epilepsy were

Table 4
Clinical characteristics, gross motor function and presence of drug resistant epilepsy in children with Congenital Zika Syndrome (n = 109). São Luís, 2016–2018.

	Drug resistant epilepsy (n = 109)				P-value
	Yes		No		
	No.	(%)	No.	(%)	
Spasticity (n = 106)					0.553[d]
No	1	33.3	2	66.7	
Yes	66	64.1	37	35.9	
Difficulty sleeping (n = 106)					0.005[c]
No	11	40.7	16	59.3	
Yes	56	70.9	23	29.1	
Irritability (n = 106)					0.007[c]
No	17	45.9	20	54.1	
Yes	50	72.5	19	27.5	
Dysphagia (n = 106)					<0.001[c]
No	19	43.2	25	56.8	
Yes	48	77.4	14	22.6	
Continuous crying (n = 106)					0.002[c]
No	21	46.7	24	53.3	
Yes	46	75.4	15	24.6	
Gross motor function classification system - GMFCS[b] (n = 101)					0.035[d]
I, II, III and IV	3	30.0	7	70.0	
V	61	67.0	30	33.0	

[a]109 children with Congenital Zika Syndrome with known data on epilepsy.
[b]GMFCS:: Levels I – walks without limitations; II – walks with limitations; III – walks using a manual mobility device; IV - self-mobility with limitations. Can use motorized mobility; V – transported in a manual wheelchair.
[c]Chi-square test.
[d]Fisher's exact test.

Table 5
Computed tomography (CT) findings of the skull and the presence of drug resistant epilepsy in children with Congenital Zika Syndrome (n = 109). São Luís, 2016–2018.

CT findings	Drug resistant epilepsy (n = 109)				P-value
	Yes		No		
	No.	(%)	No.	(%)	
Brain calcifications (n = 107)					0.704[c]
No	4	57.1	3	42.9	
Yes	64	64.0	36	36.0	
Prevalence of calcifications (n = 99)					0.194[c]
Corticals or subcortical	41	60.3	27	39.4	
Periventricular	1	33.3	2	66.7	
Thalamus, basal/diffuse ganglia	21	75.0	7	25.0	
Ventriculomegaly (n = 106)					0.027[c]
No	4	33.3	8	66.7	
Yes	63	67.0	31	33.0	
Reduced cerebral parenchyma (n = 105)					0.036[b]
No	5	35.7	9	64.3	
Yes	61	67.0	30	33.0	
Malformation of cortical development (n = 105)					0.805[b]
No	13	59.1	9	40.9	
Yes	53	63.9	30	36.1	
Cerebellar hypoplasia or malformation (n = 106)					0.022[c]
No	49	57.6	36	42.4	
Yes	18	85.7	3	14.3	
Brainstem hypoplasia or malformation (n = 104)					0.275[c]
No	52	59.8	35	40.2	
Yes	13	76.5	4	23.5	
Agenesis or dysgenesis of the corpus callosum (n = 106)					0.453[c]
No	64	65.3	34	34.7	
Yes	4	50.0	4	50.0	

[a]109 children with Congenital Zika Syndrome with known data on epilepsy.
[b]Chi-square test.
[c]Fisher's exact test.

Table 6
Ophthalmic lesions and presence of drug resistant epilepsy in children with Congenital Zika Syndrome ($n = 109$). São Luís, 2016–2018.

Ophthalmic injuries	Drug resistant epilepsy ($n = 109$)				P-value
	Yes		No		
	No.	(%)	No.	(%)	
Any ophthalmic lesion ($n = 109$)					0.004[b]
No	34	79.1	9	20.9	
Yes	34	51.5	32	48.5	
Damage to the anterior segment of the eye ($n = 98$)					0.155[c]
No	57	61.3	36	38.7	
Yes	5	100.0	0	0.0	
Chorioretinal scar ($n = 98$)					0.002[c]
No	42	55.3	34	44.7	
Yes	20	90.9	2	9.1	
Mobilization of retinal pigment ($n = 98$)					0.170[b]
No	44	59.5	30	40.5	
Yes	18	75.0	6	25.0	
Optic nerve atrophy ($n = 98$)					0.184[c]
No	47	59.5	32	40.5	
Yes	15	78.9	4	21.1	
Optic nerve hypoplasia ($n = 98$)					0.649[c]
No	58	62.4	35	37.6	
Yes	4	80.0	1	20.0	
Bilateral retinal damage ($n = 98$)					0.075[c]
No	45	58.4	32	41.6	
Yes	17	80.9	4	19.1	
Bilateral optic nerve damage ($n = 98$)					0.186[c]
No	48	60.0	32	40.0	
Yes	14	77.8	4	22.2	

[a]109 children with Congenital Zika Syndrome and known epilepsy data.
[b]Chi-square test.
[c]Fisher's exact test.

Table 7
Mean head circumference Z scores at birth, 6, 12, 24 and 36 months of age according to drug resistant epilepsy in children with Congenital Zika Syndrome. São Luís, 2016–2018.

Z-scores	Drug resistant epilepsy ($n = 107$)[a]				P-value
	Yes		No		
	n	Mean	n	Mean	
Head circumference for age					
Birth ($n = 92$)	58	−3.11	34	−2.38	0.037[b]
6 months ($n = 54$)	35	−6.30	19	−4.67	0.010[b]
12 months ($n = 72$)	48	−5.88	24	−4.69	0.024[b]
24 months ($n = 91$)	57	−5.53	34	−4.71	0.715[b]
36 months ($n = 43$)	28	−5.56	15	−4.98	0.437[b]
Weight for age					
Birth ($n = 100$)	63	−0.93	37	−0.66	0.257[b]
6 months ($n = 57$)	39	−1.43	18	−0.76	0.044[c]
12 months ($n = 72$)	48	−1.21	24	−1.18	0.943[b]
24 months ($n = 95$)	59	−1.85	36	−1.73	0.744[b]
36 months ($n = 43$)	28	−2.42	15	−1.38	0.042[b]
Weight for length					
Birth ($n = 79$)	51	−0.67	28	−0.60	0.794[b]
6 months ($n = 50$)	34	0.16	16	0.22	0.596[c]
12 months ($n = 67$)	45	−0.67	22	−0.67	0.997[b]
24 months ($n = 89$)	55	−1.39	34	−1.21	0.643[b]
36 months ($n = 41$)	26	−2.03	15	−0.95	0.909[b]
Length for age					
Birth ($n = 79$)	51	−1.51	28	−1.21	0.435[b]
6 months ($n = 50$)	34	−2.06	16	−1.34	0.188[b]
12 months ($n = 67$)	45	−1.42	22	−1.30	0.777[b]
24 months ($n = 89$)	55	−1.71	34	−1.65	0.464[b]
36 months ($n = 42$)	27	−1.83	15	−1.34	0.242[b]

[a] Of the 109 children with CZS and known epilepsy data, 2 were excluded from the growth analysis because they had hypertensive hydrocephalus at birth.
[b] Independent sample T test.
[c] Mann Whitney test.

medicated, of which 56% received two or more ASM and in 65% of them there was remission of the seizures [20]. In children followed up to 24 months of age, only 46.1% of participants with epilepsy responded to anticonvulsant treatment [19]. At 36 months of age, response to medications dropped to 32% and 81.6% of children received two or more ASM.

The most important factor in choosing ASM is the type of seizure or epileptic syndrome. Other important factors are efficacy and tolerability, half-life, potential for drug interactions, and cost [21]. The first-choice ASM in children with CZS and drug resistant epilepsy up to 36 months of age were vigabatrin, cannabidiol, topiramate, phenobarbital and valproate. In a study with children with CZS under three months of age, phenobarbital was the drug of choice, being later replaced by valproate in most cases. Above three months, valproate was started alone or in combination with a benzodiazepine, followed by levetiracetam and vigabatrin [19]. CBD has trends in the literature for long-term efficacy for seizure control in populations with significant drug resistant epilepsy, however, generalizability of these results is not possible. CDB efficacy and safety in pediatrics need stronger scientific evidence [22–24].

In the first two years of life, the most common type of seizure reported in children with CZS was epileptic spasm without hypsarrhythmia, and the rate of seizure remission was low [19]. This is the most common type of epilepsy in studies with younger children [8]. At this study, epileptic spasms were observed in almost all children in the sample. After 12 months of life, seizures most commonly present as focal and tonic [8,19]. The types of epileptic seizures that were associated with drug resistant epilepsy at 36 months of follow-up were focal seizures from the occipital lobe, generalized tonic and generalized tonic-clonic seizures. We believe that focal seizures were not more common in drug resistant epilepsy at 36 months due to increased seizure severity.

The association between microcephaly at birth, severe microcephaly at birth and excess nuchal skin with drug resistant epilepsy is evident. Intrauterine changes related to ZIKV infection are manifested in later postnatal stages, especially during the first months of life, when the highest peak of human growth is expected [5]. It is possible that the reduction in head circumference in children over time – up to at least 12 months of age – and its association with drug resistant epilepsy is related to brain disruption sequence [25] and results from the lasting effects of death and/or damage to neural stem cells in utero that impact postnatal neurogenesis, the possibility of persistence of viral replication, or continued inflammation in the brain tissues of these children [26–29].

The choice for elective surgical delivery is a risk factor for preterm delivery, which in turn is associated with respiratory and neurological problems in children [30]; despite this evidence, in this study there was no association between type of delivery or preterm delivery and the presence of drug resistant epilepsy. The positive PRNT result was also not more frequent in children with drug resistant epilepsy, probably due to false-negative results in children with clinical signs of SZC when collected in periods that exceed the period of positivity of qRT-PCR [11].

Difficulty sleeping, irritability, continuous crying, and dysphagia were clinical signs associated with drug resistant epilepsy. Children with irritability may develop clinical or subclinical seizures and clinical cases with severe brain malformations are more likely to also have epileptiform discharges and reduced sleep-related oscillations [31].

In a study with a 43 patients' sample, no associations were found between the degree of gross motor function and drug resistant epilepsy [4], which differs from the present study. With a larger sample, it was possible to observe the association, considering that the worst gross motor function and the presence of epilepsy can occur simultaneously [32] and are related to the developmental deficit of the cortical structure of these children [7].

The CT findings associated with drug resistant epilepsy are ventriculomegaly, reduced brain parenchyma, and cerebellar hypoplasia or malformation. Increased cortical thickness, brain surface anomalies [7]

and reduced parenchymal volume [31] are associated with the development of epilepsy and clinical changes in patients with CZS. In a study with 47 children with CZS, 58% of individuals with clinical epilepsy were born with malformations in the hindbrain (cerebellum and brainstem), while none of the individuals without epilepsy showed macroscopic abnormalities in this region [31]. There is an association between drug resistant epilepsy and severity of tomographic findings [4], which explains the high prevalence of this finding in this cohort.

The presence of any ophthalmic lesion and chorioretinal scar were associated with drug resistant epilepsy in our series. Ophthalmological and neurological findings are both related as consequences of congenital ZIKV infection [33,34]. Low vision may be present even without the presence of eye abnormalities, which may be related to brain damage [35].

Children with severe CZS may be at risk for malnutrition and stunting with advancing age [2]. The greater the neurological impairment, the greater the impact on growth [36]. In our study, there were significant differences in the Z-scores of weight for age of children at six and 36 months, when comparing the groups with and without drug resistant epilepsy, however, this difference dissipated over time.

5. Conclusion

The prevalence of epilepsy in children up to 36 months with CZS was 92% and 68% of these were drug resistant. Drug resistant epilepsy was associated with ventriculomegaly, reduction of brain parenchyma, damage to the cerebellum and chorioretinal scar. It was also associated with irritability, continuous crying, difficulty sleeping and dysphagia. At 36 months of age, the response to ASM was lower and the amount of ASM used was greater, when compared with shorter follow-up studies.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This research had the support of the Department of Science and Technology of the Brazilian Ministry of Health, the Maranhão State Health Secretariat, the National Council for Scientific and Technological Development (CNPq in the Portuguese acronym), the Coordination for the Improvement of Higher Education Personnel (CAPES in the Portuguese acronym) and the Foundation for the Support of Research and Scientific and Technological Development of Maranhão (FAPEMA in the Portuguese acronym).

References

[1] Brasil. Ministério da Saúde. Secretaria de vigilância em saúde. Vírus Zika no Brasil: a resposta do SUS [recurso eletrônico]. 2017. https://bvsms.saude.gov.br/bvs/publicacoes/virus_zika_brasil_resposta_sus.pdf [accessed 31 Dec. 2021].
[2] Oliveira-Filho J, Felzemburgh R, Costa F, Nery N, Mattos A, Henriques DF, et al. Seizures as a complication of congenital Zika syndrome in early infancy. Am J Trop Med Hyg 2018;98:1860–2. https://doi.org/10.4269/ajtmh.17-1020.
[3] Alves LV, Di D, Sousa Cruz C, Campos Van Der Linden AM, Rodrigues Falbo A, Gonçalves De Mello MJ, et al. Crises epilépticas em crianças com síndrome congênita do Zika vírus. Rev Bras Saúde Matern Infant 2016:33–7. https://doi.org/10.1590/1806-93042016005100003.
[4] Nunes ML, Esper NB, Franco AR, Radaelli G, Soder RB, Bomfim R, et al. Epilepsy after congenital Zika virus infection: EEG and neuroimaging features. Seizure 2021; 84:14–22. https://doi.org/10.1016/j.seizure.2020.11.004.
[5] Quilião ME, Venancio FA, Mareto LK, de Almeida Metzker S, do Nascimento AI, Vitorelli-Venancio DC, et al. Neurological development, epilepsy, and the pharmacotherapy approach in children with congenital Zika syndrome: results from a two-year follow-up study. Viruses 2020;12. https://doi.org/10.3390/v12101083.
[6] Kwan P, Schachter SC, Brodie MJ. Drug-resistant epilepsy. N Engl J Med 2011;365: 919–26. https://doi.org/10.1056/NEJMra1004418.
[7] Maia CQ, Lima WG, Nizer WS da C, Ferreira JMS. Epilepsy in children with congenital Zika syndrome: a systematic review and meta-analysis. Epilepsia 2021: 1–15. https://doi.org/10.1111/epi.16890.
[8] Krueger M.B., Câmara Magalhães S., Pessoa A., Bueno C., Rodrigues Masruha M., Sobreira-Neto A.. Electrical status epilepticus during sleep in patients with congenital Zika virus syndrome: an unprecedented clinical finding 2020. 10.1016/j.seizure.2020.08.019.
[9] Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Hauser WA, Mathern G, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc task force of the ILAE commission on therapeutic strategies. Epilepsia 2010;51:1069–77. https://doi.org/10.1111/j.1528-1167.2009.02397.x.
[10] Cavalcante TB, Ribeiro MRC, Sousa P da S, Costa E de PF, Alves MTSS de Be, Simões VMF, et al. Congenital Zika syndrome: growth, clinical, and motor development outcomes up to 36 months of age and differences according to microcephaly at birth. Int J Infect Dis 2021;105:399–408. https://doi.org/10.1016/j.ijid.2021.02.072.
[11] Batista FL, Costa EPF, Alves MTSSB, Amaral A, Borges MCR, Takahasi EHM, et al. Plaque Reduction Neutralization Test (PRNT) in the congenital Zika syndrome: positivity and and imaging characteristics. Viruses 2020;40. https://doi.org/10.3390/v12111244.
[12] Mendes AKT, Ribeiro MRC, Lamy-Filho F, Amaral GA, Borges MCR, Costa LC, et al. Congenital Zika syndrome: association between the gestational trimester of maternal infection, severity of brain computed tomography findings and microcephaly at birth. Rev Inst Med Trop Sao Paulo 2020;62:1–8. https://doi.org/10.1590/S1678-9946202062056.
[13] Pena SDJ, Shokeir MHK. Syndrome of camptodactyly, multiple ankyloses, facial anomalies, and pulmonary hypoplasia: a lethal condition. J Pediatr 1974;85: 373–5. https://doi.org/10.1016/S0022-3476(74)80119-8.
[14] Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. Dev Med Child Neurol 1997;39:214–23. https://doi.org/10.1111/j.1469-8749.1997.tb07414.x.
[15] Hiratuka E, Matsukura TS, Pfeifer LI. Cross-cultural adaptation of the gross motor function classification system into brazilian-portuguese (GMFCS). Rev Bras Fisioter 2010;14:537–44. https://doi.org/10.1590/S1413-35552010000600013.
[16] Villar J, Cheikh Ismail L, Victora CG, Ohuma EO, Bertino E, Altman DG, et al. International standards for newborn weight, length, and head circumference by gestational age and sex: the newborn cross-sectional study of the INTERGROWTH-21st project. Lancet 2014;384:857–68. https://doi.org/10.1016/S0140-6736(14)60932-6.
[17] WHO Multicentre Growth Reference Study Group. WHO child growth standards: length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age: methods and development. Geneva: World Health Organization; 2006. https://apps.who.int/iris/bitstream/handle/10665/43413/924154693X_eng.pdf. [accessed 31 Aug. 2022].
[18] WHO Multicentre Growth Reference Study Group. WHO child growth standards: head circumference-for-age, arm circumference-forage, triceps skinfold-for-age and subscapular skinfold-for-age: methods and development. Geneva: World Health Organization; 2007. https://apps.who.int/iris/bitstream/handle/10665/43706/9789241547185_eng.pdf?sequence=1&isAllowed=y. [accessed 31 Aug. 2022].
[19] Durce M, Carvalho CG, Ximenes RAA, Montarroyos UR, da Silva PFS, et al. Early epilepsy in children with Zika-related microcephaly in a cohort in Recife, Brazil: characteristics, electroencephalographic findings, and treatment response. Epilepsia 2020;61:509–18. https://doi.org/10.1111/epi.16444.
[20] van der Linden H, Carvalho MD, van der Linden V, Lacerda KM, Pessoa A, Carneiro ML, et al. Epilepsy profile in infants with congenital Zika virus infection. N Engl J Med 2018;379:891–2. https://doi.org/10.1056/NEJMc1716070.
[21] Singh R, Chakravarty K, Baishya J, Goyal MK, Kharbanda P. Management of refractory epilepsy. Int J Epilepsy 2020;6:15–23. https://doi.org/10.1055/s-0040-1712777.
[22] Patel S, Grinspoon R, Fleming B, Skirvin LA, Wade C, Wolper E, et al. The long-term efficacy of cannabidiol in the treatment of refractory epilepsy. Epilepsia 2021; 62:1594–603. https://doi.org/10.1111/EPI.16936.
[23] Raucci U, Pietrafusa N, Paolino MC, di Nardo G, Villa MP, Pavone P, et al. Cannabidiol treatment for refractory epilepsies in pediatrics. Front Pharmacol 2020;11(1). https://doi.org/10.3389/fphar.2020.586110.
[24] Moreira GA, Moraes Neto R, Ribeiro RG, Crippa ACDS. Cannabidiol for the treatment of refractory epilepsy in children: a critical review of the literature. Rev Paul Pediatr 2022;41. https://doi.org/10.1590/1984-0462/2023/41/2021197.
[25] Moore CA, Weaver DD, Bull MJ. Fetal brain disruption sequence. J Pediatr 1990; 116:383–6. https://doi.org/10.1016/S0022-3476(05)82825-2.
[26] Bhatnagar J, Rabeneck DB, Martines RB, Reagan-Steiner S, Ermias Y, Estetter LBC, et al. Zika virus RNA replication and persistence in brain and placental tissue. Emerg Infect Dis 2017;23:405–14. https://doi.org/10.3201/eid2303.161499.
[27] Aid M, Abbink P, Larocca RA, Boyd M, Nityanandam R, Nanayakkara O, et al. Zika virus persistence in the central nervous system and lymph nodes of rhesus monkeys. Cell 2017;169:610–20. https://doi.org/10.1016/j.cell.2017.04.008. . e14.
[28] Lima MC, de Mendonça LR, Rezende AM, Carrera RM, Aníbal-Silva CE, Demers M, et al. The transcriptional and protein profile from human infected neuroprogenitor cells is strongly correlated to zika virus microcephaly cytokines phenotype evidencing a persistent inflammation in the CNS. Front Immunol 2019;10. https://doi.org/10.3389/fimmu.2019.01928.
[29] de Oliveira DN, Lima EO, Melo CFOR, Delafiori J, Guerreiro TM, Rodrigues RGM, et al. Inflammation markers in the saliva of infants born from Zika-infected mothers: exploring potential mechanisms of microcephaly during fetal

development. Sci Rep 2019;9:13606. https://doi.org/10.1038/s41598-019-49796-5.

[30] De Oliveira RR, Melo EC, Falavina LP, Mathias TADF. The growing trend of moderate preterm births: an ecological study in one region of Brazil. PLoS One 2015;10:1–11. https://doi.org/10.1371/journal.pone.0141852.

[31] Sequerra EB, Rocha AJ, Medeiros GOCD, Neto MM, Maia CRS, Arrais NMR, et al. Association between brain morphology and electrophysiological features in congenital Zika virus syndrome: a cross-sectional, observational study. EClinicalMedicine 2020;000:100508. https://doi.org/10.1016/j.eclinm.2020.100508.

[32] Pessoa A, van der Linden V, Yeargin-Allsopp M, Carvalho MDCG, Ribeiro EM, van Naarden Braun K, et al. Motor abnormalities and epilepsy in infants and children with evidence of congenital Zika virus infection. Pediatrics 2018;141:S167–79. https://doi.org/10.1542/PEDS.2017-2038F.

[33] Marques V de M, Santos CS, Santiago IG, Marques SM, Nunes Brasil M das G, Lima TT, et al. Neurological complications of congenital Zika virus infection. Pediatr Neurol 2019;91:3–10. https://doi.org/10.1016/j.pediatrneurol.2018.11.003.

[34] De Paula Freitas B, De Oliveira Dias JR, Prazeres J, Sacramento GA, Ko AI, Maia M, et al. Ocular findings in infants with microcephaly associated with presumed zika virus congenital infection in Salvador, Brazil. JAMA Ophthalmol 2016;134:529–35. https://doi.org/10.1001/jamaophthalmol.2016.0267.

[35] Verçosa I, Carneiro P, Verçosa R, Girão R, Ribeiro EM, Pessoa A, et al. The visual system in infants with microcephaly related to presumed congenital Zika syndrome. J AAPOS 2017;21:300–4. https://doi.org/10.1016/j.jaapos.2017.05.024. e1.

[36] Prata-Barbosa A, Martins MM, Guastavino AB, da Cunha AJLA, Prata-Barbosa A, Martins MM, et al. Effects of Zika infection on growth. J Pediatr 2019;95:30–41. https://doi.org/10.1016/j.jped.2018.10.016 (Rio J).