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MICROCEPHALY IN THE BRAZILIAN NORTHEAST: INVESTIGATION OF POSSIBLE CORRELATED FACTORS

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ABSTRACT

The Brazilian northeast presented an outbreak of children born with Microcephaly that in August 2015 through April 2016 (Brasília, 2015). Microcephaly is a congenital anomaly associated with brain damage. The Zika virus has, until now, been indicated as the main agent causing these anomalies. This work is a cross-sectional descriptive and analytical study of the retrospective type. As data source, the database of the Epidemiological Surveillance Rapid Response of the Ministry of Health was used based on the notifications made at the biggest maternity hospital in the state. A logistic regression model was used to analyze the data. This sample included 98 mothers of babies with microcephaly. Data analysis showed that the variables that contribute most to classify the individuals regarding the diagnosis of Microcephaly were Mother with IgG positive for Cytomegalovirus and Mother with IgG positive for Toxoplasmosis. Thus, the imminence of a public health crisis requires using statistical tools for decision making to define the adequate strategy in regions where the access to serological and viral identification tests is hard.

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INTRODUCTION

Microcephaly is a clinical finding represented by a significant reduction of the head circumference. This decrease is currently quantified as 3 standard deviations bellow recommended head circumference in relation to the gestational age and child's sex. These parameters follow the updated international patterns of fetal and neonatal growth (INTERGROW 21 Century).

Microcephaly has a heterogeneous pathogenesis caused by different factors to changes in the neurological development of the child. These factors include maternal infections, such as Toxoplasmosis, Cytomegalovirus, Herpes Virus, Rubella, Human Immunodeficiency Virus (HIV), Zika Virus (ZIKV), although the latter is still in confirmatory process (NUNES *et al*, 2016). The incidence of microcephaly varies from one in every 6250 to 8500 live births recorded in some developed countries (ASHWAL, 2009).

Between the years 2000 and 2014, with 2,464 records, this finding presented an annual average of 164 cases in Brazil. And in the following year, in 2015, its prevalence increased considerably little more than nine times in relation to this annual average, registering 1,608 cases. Of this total, 1,142 were children of women residing in the Northeast region of the country, with the states of Pernambuco, Sergipeand Paraíba presenting the highest prevalence of microcephaly at birth (MARINHO *et al*, 2016). Given this outbreak of births of children with microcephaly, clinical and epidemiological studies were necessary to establish the extent of the problem, with an existing pressure that is understandable by the Brazilian population, in particular women of childbearing age, for answers. Paraíba is one of eight states of the Brazilian Northeast in the center of the epidemic. It has an area of 56,584 km² and a population of 3,914,318 inhabitants.Of approximately 2,900 suspected cases reported in 20 Brazilian states, the majority was notified in the Northeast Region (86.3%) and almost 500 only in the state of Paraíba, with the first documentation of the presence of ZIKV in amniotic fluid of two fetuses presenting intrauterine microcephaly in a municipality in Paraíba (CALVET *et al*, 2016). In this period, the largest maternity hospital in the capital of the state, Cândida VargasInstitute, notified and investigated all children with head circumference below the standards and performed test to rule out or confirm brain damage associated with microcephaly. Detailing the research required questions based on the presence of exanthematous diseases and signs and symptoms of arboviroses. From this problem, this study aimed to: (1) evaluate the factors involved in the diagnosis of microcephaly in the Northeast region during the period from August 2015 to April 2016, in a national emergency of microcephaly in the Brazilian northeast in a maternity hospital of the state of Paraíba and (2) describe serologic results of children identified with microcephaly from the measurement of the HeadCircumference.

METHODOLOGY

This work is a cross-sectional, descriptive and analytical study of the retrospective type. The data source used was the database of Epidemiological Surveillance Rapid Response of the Ministry of Health from the notifications ofCândida Vargas Institute during the Public Health Emergency that happened in August 2015 through April 2016 (Brasilia, 2015). The Cândida Vargas Institute is a maternity hospital located in João Pessoa - Paraíba, and is considered the largest maternity hospital of the state. It presents about 500 births per month and is the reference center in care for premature and risk pregnancy of the state (DATASUS, 2012).

from laboratory tests. The outcome variable considered was the Presence of Microcephaly in the Child, whose diagnosis was established based on the criteria set initially by the Ministry of Health, which stated the cutoff point of 32 cm for full-term children and the curve of Fenton classified in premature children below 37 weeks of gestational age. Frame 1 exposes the other variables studied, considered as independent variables.

Frame 1. Relation of variables that make up the data base studied in the present research

Newborn	MOTHER
City of birth	Toxoplasmosis IgG
Weight (g)	Toxoplasmosis IgM
Stature (cm)	Rublla IgG
Head Circumference (cm)	CytomegalovirusIgG
Calcification	CytomegalovirusIgM
Hydrocephalus	Herpes Virus IgG
Toxoplasmosis IgG	Dengue IgM
Rubella IgG	Chikngunya IgG
Cytomegalovirus IgG	Exanthem
Herpes Virus IgG	
Chikungunya IgG	
Zika PCR	

The data analysis was performed using the R software, which is free access, widely used in the statistics by enabling simple and effective data management and analysis (SILVA, DINIZ, BORTOLUZZI, 2009).The analysis used the Logistic Regression, which is a regression model that considers, in its structure, a set of explanatory variables (continuous or categorical) and a dependent variable (a predictor, response variable), of dichotomous and categorical nature (FIELD, 2009).This model was the most appropriate for modeling the response variable that has dichotomous character, classified as "yes" or "no" regarding the diagnosis of microcephaly. Due to the nature of the data, some the levels of certain co-variables required modification to allow adjusting a regression model without the need to remove a large amount of observations. Variables presenting p-value of 5% ($p<0.05$) in the analysis were considered significant. Ninety-eight mothers of babies notified with microcephaly were observed, and 43.6% of their children were male and 56.4%, female. The gestational age at birth varied from 30 to 41 weeks, with an average of 38 weeks. In addition, the weight of the children at birth presented an average of 2,750 g. The analysis of the coefficient of variation (CV) showed that Weight, Stature and Head circumference presented a rate of small variability with CV< 0.30, and may be summarized in a single set, with similar characteristics (Table 1).

Table 1: Description of the variables Weight (g), Stature (cm) and Head Circumference (cm) of the children in this study

Descriptive analysis of the quantitative variables

	Min	1Q	Median	Mean	3Q	Max	CV
Weight	1040	2454	2690	2750	3115	3980	0.22
Stature	37.00	44.62	47.00	46.29	48.00	51.00	0.06
Head Cirucmference	25.00	30.00	31.00	30.54	32.00	33.00	0.06

This study included all children with microcephaly notified during the period of the outbreak. However, cases lacking data and complementary tests were excluded. In this way, the sample included 98 of 144 the notified cases. Each mother-child dyad, at the time of notification and at birth, underwent serology tests for Toxoplasmosis, Rubella, Cytomegalovirus, Herpes Virus, Syphilis, Dengue and Chikungunya, obtained

Thus, this homogeneity of data can be demonstrated with few discrepant cases in relation to weight, stature and head circumference in the compound boxplots in Figure 1, 2 and 3. Figure 03 shows the presence of asymmetry of data on the left, thus showing a concentration of head circumference of 30 through 32 cm, with 55% of children with brain injury.

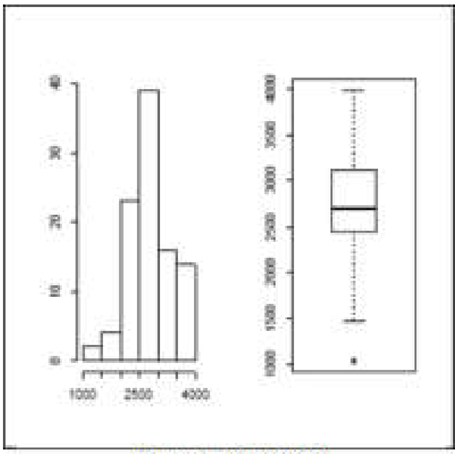

Figure 1 - NB Weight

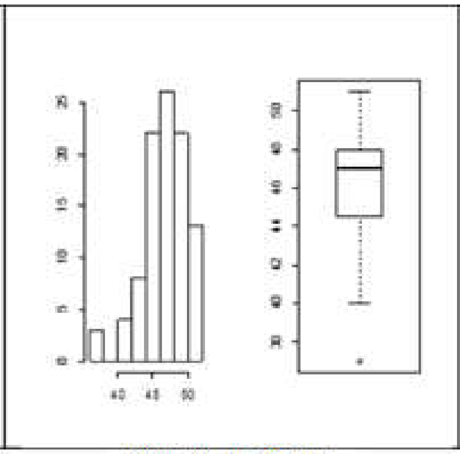

Figure 2 - NB Stature

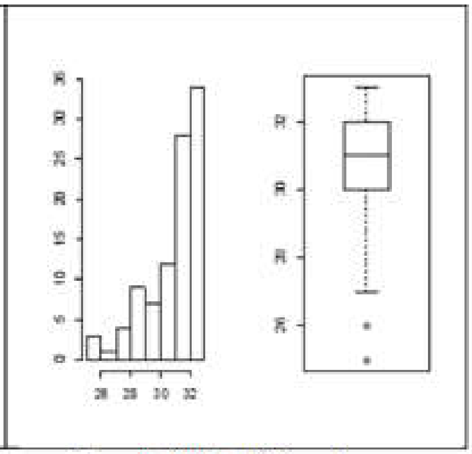

Figure 3 - NB Head Circumference

Table 2. Estimates of coefficients, standard error and p-value of the adjusted model

Variables	Estimated Coefficients	Standard Erro	p-value	Odds (exp Beta)
Interceptor	53.8868	13.4458	<0.001	
Head Circumference	-1.792	0.4395	<0.001	0.1666
MotherCytoIGG	3.7609	0.9904	<0.001	42.9871
MotherToxoIGG	2.7634	1.1903	<0.020	15.8537

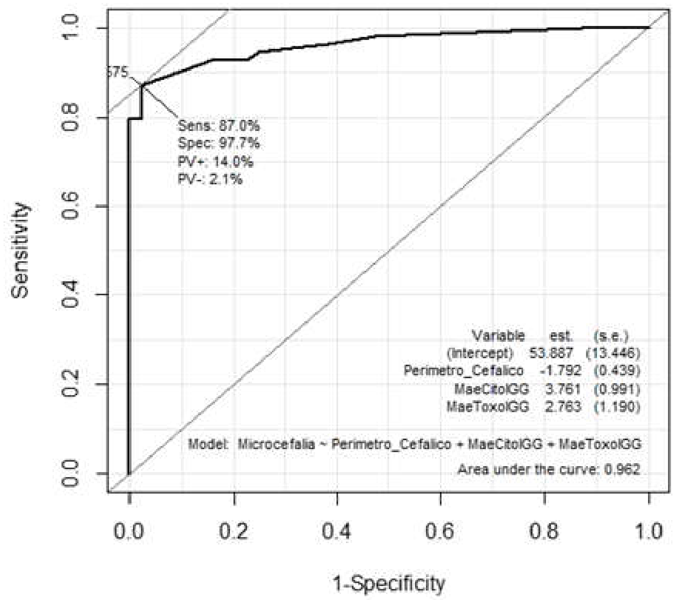

Figure 4. Curve ROC adjusted model

With respect to classification of microcephaly defined by Intergrowth 21 century table, 41% of children reported, investigated and confirmed with brain injury in this service were defined below 3 standard deviations. After analysis, the relationship between history of exanthematic disease during pregnancy, as anamnesis, at the time of notification associated with decreased head circumference, mothers with positive serology for toxoplasmosis and cytomegalovirus IgG were the variables that become more relevant and had high sensitivity and specificity for the confirmation of microcephaly. (Figure 4). Table 2 shows the estimates, standard errors and p-values used to determine the significance of the estimates in the proposed model. The presented results evidenced that all coefficients are statistically different from zero (p-values of the coefficients smaller than 0.05). I.e., such variables, including the interaction between them, are relevant to explain the outcome in question. The analysis of the coefficients shows that the co-variables that contribute most to classify the individuals regarding the diagnosis of Microcephaly are Mother with IgGPositive for Cytomegalovirus and Mother with IgGPositive for Toxoplasmosis, due to the high values of the estimates of the parameters associated with these co-variables. From the adjusted Odds Ratios, sensitivity and specificity, when including characteristics of immunity to toxoplasmosis, cytomegalovirus and maternal background of exanthematic disease, were 87% and 97.7%, respectively. The variables Mother with IgG Positive for Cytomegalovirus and Mother with IgGPositive for Toxoplasmosis showed a positive effect on the outcome, i.e., increasing the child's chances of microcephaly diagnosis.

RESULT AND DISCUSSION

From the data presented, one can question the need to conceptualize microcephaly and the importance of a detailed anamnesis during pregnancy regarding the signs and symptoms of congenital infection during prenatal (ARAÚJO, 2016). Descriptive data of the present study corroborate partially the study performed by Vargas *et al*. (2016), which described 40 cases of children diagnosed with microcephaly possibly related to ZIKV reported to the State Health Department of Pernambuco, during the August and October 2015.These authors observed that the median of the head circumference was 31 cm (Min:21cm and Max: 35.5 cm), of the stature 46 cm (Min:23 cm and Max:49.5 cm) and of the weight 2,628g (Min: 810g and Max: 3,450g). Furthermore, among the 40 cases of children with microcephaly, 20 were males, 19 females and 1 had indefinite genitalia. In this study, only 41% of children with brain injury confirmed by imaging tests were classified as microcephaly by the international classification. Therefore, we need to consider other aspects relevant for the research. Epidemiological history, and maternal serology become relevant. The observations relating to anthropometry of the present study deserve special mention, especially the low median of birth weight, because studies show that the origin of the health and disease development may be a reflection of environmental influence. Thus, the habits and customs of the pregnant woman can influence the outcome, which is a newborn with microcephaly associated with low birth weight (GILLMAN, 2005).

Regarded as a sign of malnutrition or deficit of brain growth, microcephaly may result from problems of genetic, chromosomal or environmental origin, including infections. Moreover, microcephaly may also result from any damage caused in the developing brain in peri- and post-natal period or at the end of gestation. Its sequels depend on the etiology and the age at which the event occurred.Thus, understanding when this child was affected is a challenge for all who investigate this sign. (EICKMANN *et al*, 2016). According to the literature, the processes caused by viral infectious diseases, such as toxoplasmosis, rubella, cytomegalovirus, herpes and syphilis, can result in microcephaly in fetuses of women who were exposed to etiologic agents during pregnancy (Vargas *et al*, 2016).However, currently, studies, such as Faria *et al*. (2016), suggest the existence of a possible relationship between ZIKV and the occurrence of microcephaly. In addition, the Oswaldo Cruz Foundation (Fiocruz), along with the Flavivirus Laboratory of the Oswaldo Cruz Institute, detected, in samples of two pregnant women from Paraíba, the presence of the genome of ZIKV, whose fetuses presented confirmation of microcephaly through ultrasonography (CALVET *et al*, 2016). However, the results presented in this work do not allow stating that the ZIKV was responsible for causing microcephaly in newborns in this institution, at least in an isolated manner. Presence of positivity for IgG specific to toxoplasmosis and cytomegalovirus, associated with the history of exanthematic disease, were important for the high percentage of sensitivity and specificity in the modeling presented.

Corroborating this, the research developed by Lucchese and Kanduc (2016) identified a set of 41 pentapeptides common to agents infected by ZIKV, Cytomegalovirus, Toxoplasmosis, which have in common the fetal microcephaly, and 37 of these occur in epitopesexperimentally valid as an immuno present in human beings.In addition, these authors suggest that the fetal neurological development can be strongly evidenced by a load of cross-reaction triggered by the ZIKV. Toxoplasmosis is one of the most widespread zoonoses in the world, having as an etiological agent *Toxoplasma gondii* (*T.gondii*). During pregnancy, the primary infection of the mother by this pathogen is of great importance, since its infection may bring serious consequences for the fetus. Therefore, the congenital toxoplasmosis ends up being regarded as an important cause of morbidity and mortality (SILVA; OKAZAKI, 2012). In the first trimester of pregnancy, this infection can cause fetus death.In the second trimester, it may cause the Sabin Tetrad, a syndrome that causes chorioretinitis, brain calcifications, mental retardation or neurological disorders and alterations of the cranial volume, with macro or microcephaly (in 50% of cases).When acquired in the third trimester of pregnancy, the child may be born normally and, only a few days, weeks or months after birth,may present evidence of disease (SOUZA *et al*., 2010). The Cytomegalovirus infection also stands out, affecting approximately two through six children every 1000 live births, which, depending on the gestational age when the infection occurs, results in severe consequences to the fetus.This type of infection is often asymptomatic and is only recognized from its manifestation in the fetus (KAGAN; HAMPRECHT, 2017). When diagnosed more severe cases of fetal infection, the child may present microcephaly, hydrocephalus, sensorium-neural deafness, intracranial calcifications, prematurity, small size for gestational age, among others (LOBATO-SILVA, 2016). Furthermore, there is history of intrauterine reactivation of infection in pregnant women with prior immunity (YAMAMOTO, 2010). In isolation, studies, such as Swanson and Schleiss (2013), show that microcephaly is one of the sequels presented by children whose mothers were infected by the Cytomegalovirus. In this study, these authors observed that 53% of the 106 children studied showed microcephaly as a sequel of congenital cytomegalovirus infection. The presence of several outbreaks of dengue can cause worsening of the disease in a same individual, we can say that this can happen overlapping other arboviroses.

Conclusion

The imminence of a public health crisis in regions with difficult structure for laboratory diagnosis requires considering epidemiological aspects and some serologic indicators. Definingthe profile of children committed using statistical tools may be an appropriate strategy in regions where access to serology and viral identification is difficult. This study evidenced investigation and special care of patients with positive serology for cytomegalovirus, toxoplasmosis and arboviroses associated with maternal background of exanthematic disease. Therefore, there may happen a reactivation of viral diseases with pre-existing immunity to toxoplasmosis or cytomegalovirus, as well as the hypothesis of co-infections. Clinical and epidemiological studies are necessary to clarify the causes of microcephaly and the relationship between microcephaly and ZIKV. To do this, some technological innovations available may be used for fast outcomes and catchment of cases in more distant areas. The non-serological confirmation, a local and swift characteristic of the outbreak, justifies continued researches in the area, as well as the national emergency of microcephaly in northeast Brazil.

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