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Microcephaly in northeastern Brazil: a review of 16 208 births between 2012 and 2015

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Abstract:

A recent outbreak of microcephaly has been reported from Northeast Brazil. Neither its aetiology, nor its clinical significance has yet been fully established. A complication from an intrauterine infection with the Zika virus (ZIKV) is, thus far, the most explored hypothesis. In Paraíba, one of the nine States within the epicentre of the epidemic, 21 medical centres collaborate, via telemedicine since 2012, in a paediatric cardiology network. The Network's database currently stores information on more than 100,000 neonates. To support the microcephaly research, from December 1st to 31st, 2015, the Network ran a task force and rescued the head circumference from 16,208 neonates. A much higher than expected incidence of microcephaly was observed, varying from 2% to 8% according to the utilized classification criteria. These findings raise questions about the condition's diagnosis and its notification. An observed presentation's seasonality might reflect that of infections carried on by the Aedis aegypti vector. However, the temporal fluctuation was documented since late 2012, before the allegedly entry of the ZIKV in Brazil, in mid-2014. Further questions are raised on both the epidemiological surveillance of the Aedis aegypti infections, as well as on different aetiological possibilities for the outbreak. At this stage, follow-up studies in the children diagnosed with microcephaly are mandatory prior to concluding what problem we are facing; how it came about and which consequences it may, or not, bring to the Brazilian population in years to come.

Introduction:

Microcephaly is a clinical finding and not a disease. It is defined as an occipital-frontal head circumference (OFC) smaller than expected for gestational age and gender. It is reported to occur in one in every 6,250 to 8,500 live births[1]. Since the growth of the cranium depends on the forces of an expanding brain, microcephaly is an indicator of an undersized brain. Whilst the measurement of OFC is a trusted assessment of intracranial brain volume, controversy exists about the lower limit for this measurement as well as for the need of ethnically controlled data[2]. Furthermore, the clinical implications of an undersized brain are far more complex to establish.

From November 2015, there has been a dramatic increase in reported numbers of microcephaly in Northeast Brazil. The public health implications could be enormous. Whilst clinical and epidemiological studies are necessary to establish the extent of the problem, there is an understandable pressure from the Brazilian population, particularly women at reproductive age, for quick answers.

The total number of cases reported with microcephaly in this period, from 20 Brazilian States, approached 3,000[3]. Over 85% of them are from the Northeast. Paraíba, one of the nine States from this Region, is second in number of reported cases. It has 21,847 mi², and a population of 3,944 millions and has reported on nearly 500 cases and first documented the presence of ZIKV in amniotic fluid from two microcephalic foetuses[4]. Also, since 2012, in collaboration with the NGO – Círculo do Coração, Paraíba runs a Paediatric Cardiology and Network[5], which among other actions, has screened and stores cardiovascular data from over 100,000 neonates.

Head circumference was not included in the original data set. However, due to the pressing needs to shed light on the microcephaly crisis, the Network proposed a four-week task force to rescue this information in 10% of the dataset. This report summarizes the results from the task force.

Methodology:

This is a descriptive, observational and transverse study, with data from the Círculo do Coração - Paediatric Cardiology and Perinatology Network (RCP-CirCor) Database from Paraíba, in Northeast Brazil.

Sample collection

Lists with ID number, mother's name and date of birth of all RCP-CirCor neonates were sent to each participant site. Nurses were advised to collect OFC and thorax circumference information from delivery room books or patient's files in 10% of

patients and to spread the search over the four-year period, to reflect the problem over time. Remaining information was retrieved from the Network's database and included mother's name and address, gestational age, gender, weight and height at birth. No funding was allocated to this task force.

Microcephaly criteria utilized

In this study, classification of microcephaly was based on three different criteria, as follows:

1. Brazilian Health Ministry proposed criteria, where microcephaly equals an OFC smaller than 32 cm for term neonates.[6]
2. Fenton curves, where microcephaly equals an OFC less than -3 standard deviation (SD) for age and gender.[7]
3. Proportionality criteria, where microcephaly equals an OFC less than ((height/2) + 10) ± 2.[8]

Microcephaly classification

Neonates were classified with microcephaly according to each one of the three criteria. A separate group was created for those who fulfilled all three criteria. Finally, those who fell into the lower third in each criterion were grouped as extreme cases of microcephaly.

Statistical analysis

The software R were used for data analysis, which included Friedman as the statistical model for hypothesis determination with the confidence interval of 95%.

Results

Between Dec 1st and 31st 2015, OFC was collected from 16,208 neonates, born between January 1st 2012 and December 31st 2015, in 21 different public health centres from Paraíba. There was an even distribution of gender, most of them were term babies, weighting over 3,000g and measuring over 45cm at birth. Table 1 describes the population.

Microcephaly classification

Depending on the criteria utilized, in this sample, from 4% to 8% of kids born between 2012 and 2015 had microcephaly. Neonates fulfilling all three criteria accounted for nearly 2% of the sample. If, however, only the extreme cases are considered, the

neonates fulfilling all three criteria fall within the expected ranges reported for microcephaly worldwide. Table 2 summarizes these findings.

Temporal distribution

The distribution of cases of microcephaly between 2012 and 2015 is observed in Fig. 1. A temporal oscillation is observed which is concordant in all three criteria. The numbers are greater than expected since the end of 2012 and with its sharpest peak in mid-2014. However when only the extreme cases of microcephaly are considered a significant (p=0.001) increase in numbers is observed in recent months as shown on Figure 2.

Discussion

In 2000, SINASC (Brazilian Live Birth Information System) reported that the prevalence of microcephaly in Brazilian newborns was 5.5 cases/ 100,000 live births and in 2010 it was 5.7 cases / 100,000 live births[7]. Over the last three monts it went up to 99.7 per 100.000 live births which corresponds to a twentyfold increase[3].
In this study, independent of the classification criteria used, we demonstrated a much higher incidence of microcephaly between 2012 and 2015.

Projecting our findings to the total number of live births in Paraíba, in 2014 (n=58,147), the number of neonates born with microcephaly in that year would have been 4,652 by the Health Ministry proposed criteria, 2,442 by the Fenton curves and 2,907 by the proportionality criteria. Neonates classified with microcephaly by all three criteria would have been 1,105.

These observations highlight the need to review the situation carefully. Many questions need to be answered prior to concluding what problem we are facing, how it came about and which consequences it is likely to bring to the Brazilian population in years to come.

The first question to be addressed is the real incidence of microcephaly in Northeast Brazil.

The discrepancy from the expected and found cases may reflect the condition's major sub-notification in the official sites in recent years coupled with an even greater epidemiological crisis than presumed or simple the need to revise the diagnostic criteria for the condition.

The numbers of very extreme cases of microcephaly, for instance, while significantly increasing over the last few months, are much smaller and until recently fell within the expected ranges for the worldwide reported incidence.

It is possible that a high incidence of milder forms microcephaly has been occurring well before the current outbreak, but that only those extreme cases, with classical phenotypes, were being notified.

And as the number of extreme cases increased over these past three or four months so did the awareness of health professionals who started to notify milder forms.

What remains to be determined is the clinical significance of these milder forms, which account for the vast majority of the reported cases. Could a 31cm or 32cm OFC in a term neonate, for instance, be within normal limits for this particular population? Could ethnical or nutritional components explain these findings? Are we facing large numbers of a neurological disease or observing an anthropometric variation of normality?

The microcephaly occurrence displays a temporal distribution. Infections caused by the Aedes aegypti, a proposed aetiology for the outbreak, also demonstrate temporal fluctuations.[9]

Currently, the association with the ZIKV infection is the most explored possibility. Evidence of perinatal transmission of ZIKV[10] together with its strong neurotropism[11] and its documentation in amniotic fluid of foetuses with microcephaly[4] are factors that favour this hypothesis. However, if the ZIKV were indeed introduced in Brazil at the World Cup in mid 2014[12], the outbreak of microcephaly would have preceded it. ZIKV has been identified in Africa over 50 years ago, and neither there nor in the outbreaks outside Africa, such an association with microcephaly has been reported[13]. However, recently ZIKV has been associated to a number of conditions including Guillain-Barrè syndrome during a recent outbreak of the infection in the French Polynesia[10].

Many other potential factors need to be considered as the cause of the outbreak. Among them figures the possibility of boosting effects from associated infections, perhaps even viral infections, such as DENV and CHIKV, both carried by the same Aedes aegypti vector. Also to be considered is teratogens exposure, such as vaccines or drugs used in early pregnancy.[1,2] Further, malnutrition, which has previously been associated to microcephaly, could have an intensifying effect when coupled with other aetiological factors. Indeed, most of the reported cases have occurred in low-income families.

Thus far, controlling the Aedes aegypti vector has been a major public health strategy, which is justified not only by its potential benefits in holding back the epidemic, which may or may not hold true, but for its numerous other benefits to the population.

We can only conclude that we are facing a new and challenging public health problem and that limited epidemiological and clinical data hinders conclusions at this early stage.

Further retrospective studies, as well as follow-up investigations on both the clear-cut microcephaly as well as the borderline or "smaller head" neonate are paramount to clarify the aetiology as well as the neurological consequences of these findings and prompt management strategies to the affected populations.

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FIGURE 1

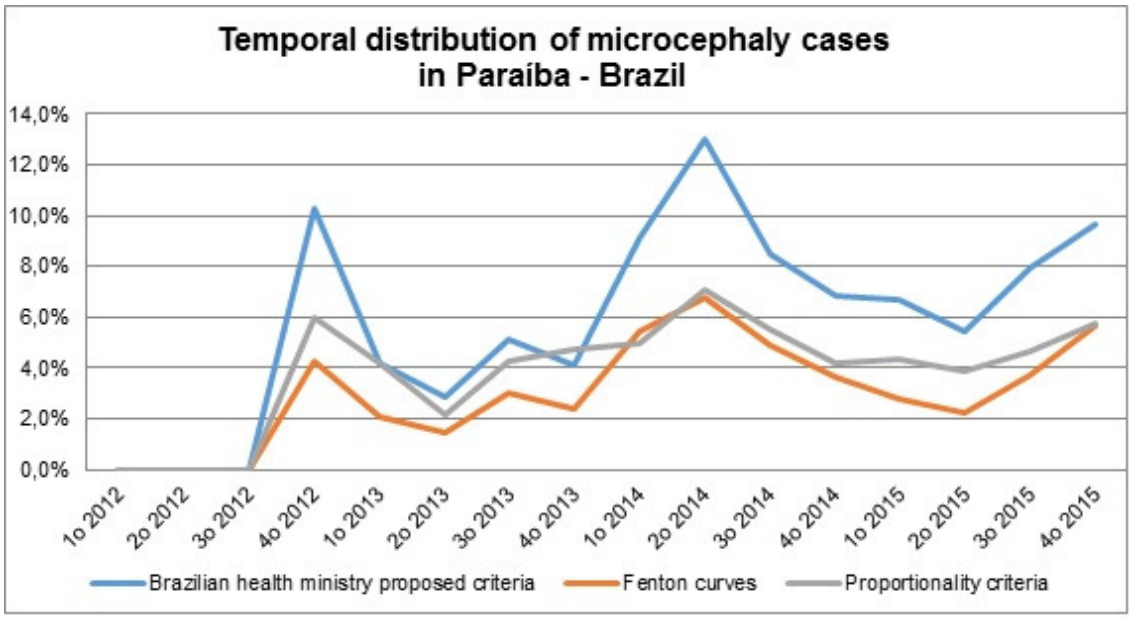

FIGURE 2

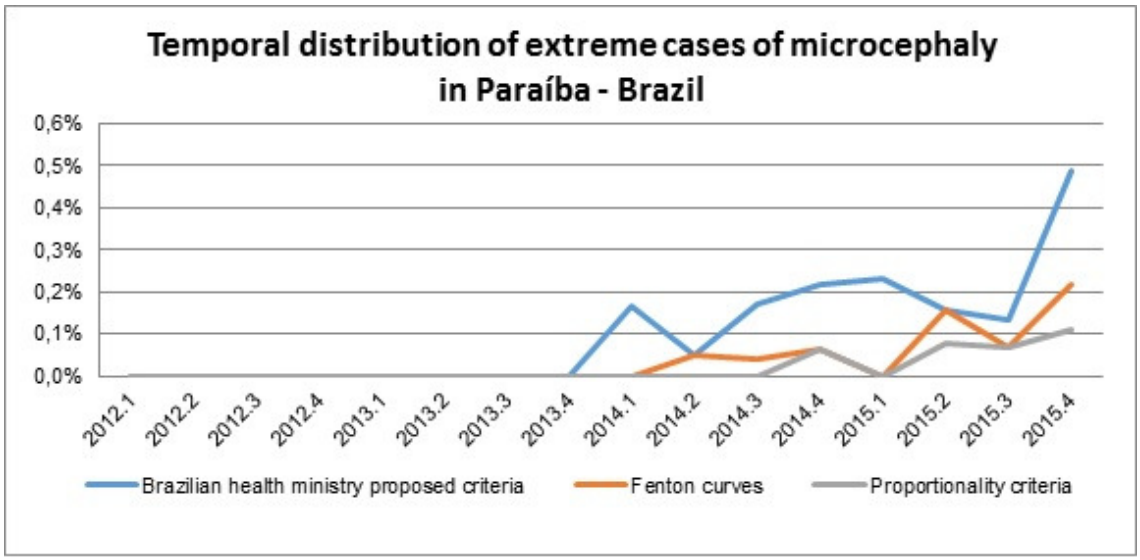

Table 1 – Neonatal profile

Profile of Neonates	n	%
Gender		
Female	7,750	47.8%
Male	8,458	52.2%
Gestational Age (weeks)		
<32	21	0.1%
32|--34	39	0.2%
34|--37	557	3.4%
>37	15,591	96.2%
Weight (g)		
<1500	37	0.2%
1500|--2000	107	0.7%
2000|--2500	731	4.5%
2500|--3000	3,187	19.7%
>3000	12,146	74.9%
Lenght (cm)		
<35 cm	9	0.1%
35|--40 cm	58	0.4%
40|--45 cm	569	3.5%
45|--50 cm	9,415	58.1%
> 50 cm	6,157	38.0%
OFC (cm)		
<= 30 cm	*229*	*1.4%*
30--|31 cm	*376*	*2.3%*
31--/32 cm	*958*	*5.9%*
32--|33 cm	*2,185*	*13.5%*
> 33cm	*12,460*	*76.9%*

Table 2 – Classification of Microcephaly

Classification	n	%
Brazilian health ministry proposed criteria		
Normal	14,909	91.99%
Microcefaly (all)	1,299	8.01%
Microcefaly (extreme)	31	0.19%
Fenton curves		
Normal	15,530	95.82%
Microcefaly (all)	678	4.18%
Microcefaly (extreme)	6	0.04%
Proportionality criteria		
Normal	15,405	95.05%
Microcefaly (all)	803	4.95%
Microcefaly (extreme)	11	0.07%
Common to the three criteria		
Normal	15,876	97.95%
Microcefaly (all)	332	2.05%
Microcefaly (extreme)	3	0.02%