

Microcephaly in Pernambuco State, Brazil: epidemiological characteristics and evaluation of the diagnostic accuracy of cutoff points for reporting suspected cases

Microcefalia no Estado de Pernambuco, Brasil: características epidemiológicas e avaliação da acurácia diagnóstica dos pontos de corte adotados para notificação de caso

Microcefalia en el estado de Pernambuco, Brasil: características epidemiológicas y evaluación de la precisión diagnóstica de los puntos de corte adoptados para la notificación de casos

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Abstract

The increase in the number of reported cases of microcephaly in Pernambuco State, and Northeast Brazil, characterized an epidemic that led the Brazilian Ministry of Health to declare a national public health emergency. The Brazilian Ministry of Health initially defined suspected cases as newborns with gestational age (GA) \geq 37 weeks and head circumference (HC) \leq 33cm, but in December 2015 this cutoff was lowered to 32cm. The current study aimed to estimate the accuracy, sensitivity, and specificity of different cutoff points for HC, using ROC curves, with the Fenton and Intergrowth (2014) curves as the gold standard. The study described cases reported in Pernambuco from August 8 to November 28, 2015, according to sex and GA categories. The Fenton and Intergrowth methods provide HC growth curves according to GA and sex, and microcephaly is defined as a newborn with HC below the 3rd percentile in these distributions. Of the 684 reported cases, 599 were term or post-term neonates. For these, the analyses with ROC curves show that according to the Fenton criterion the cutoff point with the largest area under the ROC curve, with sensitivity greater than specificity, is 32cm for both sexes. Using the Intergrowth method and following the same criteria, the cutoff points are 32cm and 31.5cm for males and females, respectively. The cutoff point identified by the Fenton method (32cm) coincided with the Brazilian Ministry of Health recommendation. Adopting Intergrowth as the standard, the choice would be 32cm for males and 31.5cm for females. The study identified the need to conduct critical and on-going analyses to evaluate cutoff points, including other characteristics for microcephaly case definition.

Microcephaly; Zika Virus Infection; Epidemiological Surveillance; Data Accuracy

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Introduction

The rapid rise in the number of suspected cases of microcephaly in live newborns starting in August 2015 in Pernambuco State, Northeast Brazil, called the attention of physicians in the public and private health care systems in that state ¹.

Alerted to the problem, the Executive Secretariat for Health Surveillance (SEVS) of the Pernambuco State Health Secretariat (SES-PE) detected a change in the pattern of occurrence of this congenital anomaly, with an increase in the number of cases when compared to previous years, thus characterizing an epidemic ².

The possible association between the increase in the number of microcephaly cases and outbreaks of Zika virus infection in Brazil since late 2014, especially in Northeast Brazil, became the object of investigation ³.

Other states of Northeast Brazil reported an increase in microcephaly cases, leading the Brazilian Ministry of Health to declare a national public health emergency on November 11, 2015 ⁴.

For reporting purposes, suspected microcephaly cases were initially defined as live newborns with gestational age ≥ 37 weeks and head circumference (HC) ≤ 33 cm ⁵. However, this cutoff point, with high sensitivity but not fully backed by the existing scientific literature ^{6,7}, generated an excessive number of notifications. Thus, as of December 2015, the Brazilian Ministry of Health established HC ≤ 32 cm as the definition of a suspected case of microcephaly ⁸.

To contribute to the discussion on the cutoff point for reporting suspected cases, the current study aimed to estimate the accuracy, sensitivity, and specificity of different cutoff points using the Fenton method and the curve proposed by the Intergrowth project ⁷ as the gold standard. The Intergrowth curve was included in the analyses because it was developed recently, based on measurements of children from countries with different ethnic and economic characteristics.

Material and methods

The study analyzed a total of 696 suspected microcephaly cases reported to the SES-PE from August 2 to November 28, 2015 (epidemiological weeks 31 to 47).

The analyses excluded newborns with no recorded information on head circumference and/or gestational age and another two cases classified as recording errors (HC = 35cm and 45cm), leaving two cases with HC = 33.5cm, identified in the sample as suspected cases of microcephaly, leaving a total of 684 suspected cases.

The study began with a description of reported cases by distributions according to sex and gestational age categories.

Gestational age (GA) categories were defined as follows: preterm neonates – GA up to 36 weeks and 6 days; term and post-term neonates – GA 37 weeks or more, in which term neonates were defined as GA up to 41 weeks and 6 days.

To classify suspected microcephaly cases as positive or negative, we first used the Fenton tables and then the Intergrowth method (2014), which provide distributions of growth curves for head circumference according to GA and sex; positive (confirmed) cases were defined as newborns with HC below the 3rd percentile of these distributions. We also analyzed the time trend in suspected and confirmed cases according to epidemiological week.

ROC (Receiver Operating Characteristic) curves were used to evaluate the cutoff points for HC. The gold standard was first the Fenton curves and then the Intergrowth tables.

The study also analyzed differences in the proportion of confirmed cases according to the Fenton curve, by sex.

The criterion for selecting the “ideal” cutoff point was maximization of the area under the ROC curve, respecting the need for greater sensitivity than specificity, given the nature of the object of investigation (screening). The analyses were performed separately according to sex and GA categories.

The Intergrowth method, at the beginning of the epidemic, only provided growth curves of HC for newborns with GA ≥ 33 weeks. For consistency, only neonates with GA ≥ 37 weeks were included in the analyses using this method.

Finally, the study verified the concordance between the classifications obtained by the two methods, using the kappa coefficient. The analyses were performed with Stata, version 12 (Stata-Corp LP, College Station, USA).

Results

Of the 684 reported cases, 599 were term/post-term neonates and 85 (12.4%) were preterm, a similar percentage to that of the general population according to the Brazilian Information System on Live Births (SINASC) for Pernambuco State in 2013. Seven preterm neonates had GA between 22 and 31 weeks. The majority of the reported cases were females (423 cases, or 62% of the total).

Classification of reported cases according to the Fenton criterion by sex and GA showed a positive rate of 39% (267 cases), leaving 417 false-

positives (61%). For the 599 neonates with GA \geq 37 weeks, the positive rate according to the Fenton criterion was 41% (243 cases), while the Intergrowth method showed 188 positive cases (31%).

The percentages of positive microcephaly cases did differ significantly according to sex: 41% for males and 38% for females ($\chi^2(1 \text{ df}) = 0.44$; $p = 0.506$).

Notwithstanding the high number of false-positives, the 267 confirmed cases according to the Fenton criterion, reported over the course of 17 epidemiological weeks, represent a relative rate of 58 cases per 10,000 live births.

Figure 1 shows the distribution of suspected and confirmed cases according to the Fenton method, by epidemiological week.

Table 1 shows the sensitivity, specificity, and accuracy using ROC curves with the two methods. According to the Fenton criterion, the cutoff point with the largest area under the ROC curve, and respecting the need for higher sensitivity than specificity, was 32cm for both sexes. However, for females this cutoff point showed a specificity of 70%, while for males it was approximately 80%.

According to the Intergrowth method, the cutoff points using the same criteria are 32cm and 31.5cm for males and females, respectively.

Concordance between the methods for both sexes was 90.8% (kappa coefficient = 0.802; $p < 0.001$). Concordance was 90.3% for males (kappa = 0.792; $p < 0.001$) and 91.2% for females (kappa = 0.809; $p < 0.001$).

Table 2 shows the classification of newborns according to cutoff points for HC identified by the two methods in the analysis of accuracy according to GA categories. For newborns with GA \geq 37 weeks, the Intergrowth method shows a false-positive rate of 11.4% (68 cases), compared to 15.7% by the Fenton method. Considering newborns of all gestational ages, there were a total of 108 false-positives (15.8%) according to the Fenton method.

Finally, considering newborns with GA \geq 37 weeks (599), a cutoff of 32cm would lead to 54% positives (324 cases), while cutoffs with higher specificity, like 31cm and 30.5cm, would lead to 29% and 20% positives, respectively.

Figure 1

Distribution of reported and confirmed cases of microcephaly according to the Fenton curve, by epidemiological week. Pernambuco State, Brazil, 2015.

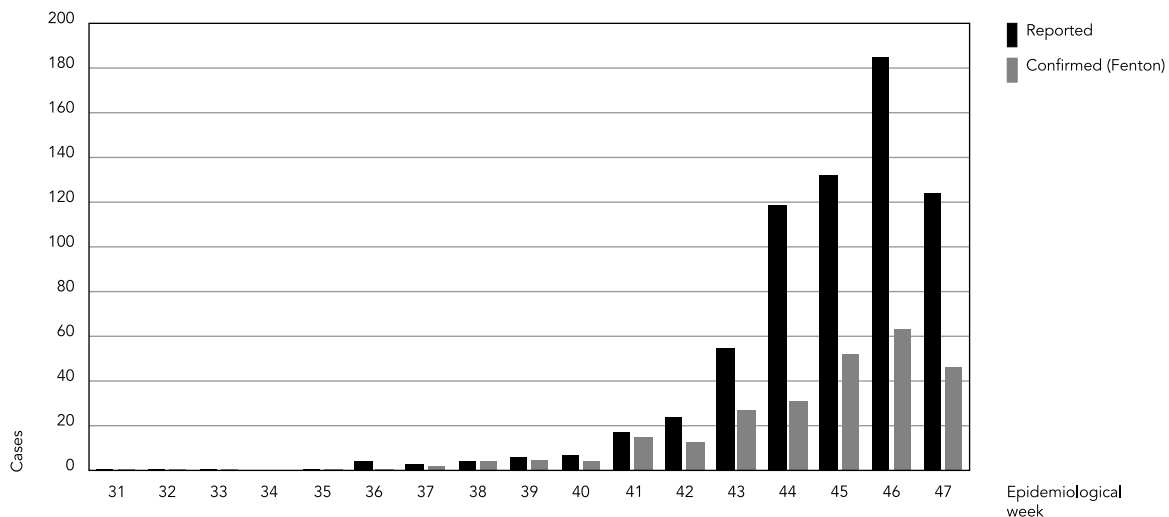


Table 1

Accuracy, sensitivity, and specificity for definition of the cutoff point for head circumference (in centimeters) with the Fenton curve and Intergrowth method as the gold standard.

Fenton					Intergrowth				
Cutoff	Sensitivity (%)	Specificity (%)	Accuracy (%)	Term/post-term newborns (both sexes)					
				Area under ROC curve (%)	Cutoff	Sensitivity (%)	Specificity (%)	Accuracy (%)	Area under ROC curve (%)
≤ 33.5	100.0	0.0	40.6	50.0	≤ 33.5	100.0	0.0	31.4	50.0
≤ 33.0	100.0	0.6	40.9	50.3	≤ 33.0	100.0	0.5	31.7	50.2
≤ 32.5	97.1	62.1	76.3	79.6	≤ 32.5	98.9	55.0	68.8	77.0
≤ 32.0	94.6	73.6	82.1	84.1	≤ 32.0	98.9	66.4	76.6	82.7
≤ 31.5	74.1	96.6	87.5	85.3	≤ 31.5	86.2	92.7	90.6	89.4
≤ 31.0	70.0	98.3	86.8	84.1	≤ 31.0	84.6	95.9	92.3	90.2
≤ 30.5	49.4	100.0	79.5	74.7	≤ 30.5	62.8	99.5	88.0	81.1
< 30.5	0.0	100.0	59.4	50.0	< 30.5	0.0	100.0	68.6	50.0

Term/post-term newborns (males)									
Cutoff	Sensitivity (%)	Specificity (%)	Accuracy (%)	Area under ROC curve (%)	Cutoff	Sensitivity (%)	Specificity (%)	Accuracy (%)	Area under ROC curve (%)
≤ 33.0	100.0	1.4	42.4	50.7	≤ 33.0	100.0	1.2	32.6	50.6
≤ 32.5	92.9	72.5	80.9	82.7	≤ 32.5	97.3	65.2	75.4	81.3
≤ 32.0	88.8	79.7	83.5	84.2	≤ 32.0	97.3	73.9	81.4	85.6
≤ 31.5	62.2	97.8	83.0	80.0	≤ 31.5	80.0	97.5	91.9	88.8
≤ 31.0	59.2	98.5	82.2	78.9	≤ 31.0	77.3	98.8	91.9	88.0
≤ 30.5	42.9	100.0	76.3	71.4	≤ 30.5	56.0	100.0	86.0	78.0
< 30.5	0.0	100.0	58.5	50.0	< 30.5	0.0	100.0	68.2	50.0

Term/post-term newborns (females)									
Cutoff	Sensitivity (%)	Specificity (%)	Accuracy (%)	Area under ROC curve (%)	Cutoff	Sensitivity (%)	Specificity (%)	Accuracy (%)	Area under ROC curve (%)
≤ 32.5	100.0	55.5	80.9	77.7	≤ 32.5	100.0	48.4	64.5	74.2
≤ 32.0	98.6	69.7	83.5	84.2	≤ 32.0	100.0	61.6	73.5	80.8
≤ 31.5	82.1	95.9	83.0	89.0	≤ 31.5	90.3	89.6	89.8	89.9
≤ 31.0	77.2	98.2	82.2	87.7	≤ 31.0	89.4	94.0	92.6	91.7
≤ 30.5	53.8	100.0	76.3	76.9	≤ 30.5	67.3	99.2	89.3	83.2
< 30.5	0.0	100.0	58.5	50.0	< 30.5	0.0	100.0	68.9	50.0

Preterm newborns (both sexes)				
Cutoff	Sensitivity (%)	Specificity (%)	Accuracy (%)	Area under ROC curve (%)
≤ 33.0	100.0	0.0	28.2	50.0
≤ 32.0	100.0	31.1	50.6	65.6
≤ 31.0	100.0	62.3	72.9	81.1
≤ 30.0	100.0	77.0	83.5	88.5
≤ 28.0	79.2	93.4	89.4	86.3
≤ 26.0	33.3	96.7	78.8	65.0
< 26.0	0.0	100.0	71.8	50.0

ROC: Receiver Operating Characteristic.

Table 2

Classification of newborns according to cutoff points adopted for head circumference (in centimeters): Fenton method, according to gestational age categories and sex; Intergrowth method, according to sex.

Fenton				Intergrowth			
Cutoff	Positive	Negative	Term/Post-term (males)		Positive	Negative	Total
			Total	Cutoff			
≤ 32 (+)	87	28	115	≤ 32 (+)	73	42	115
> 32 (-)	11	110	121	> 32 (-)	2	119	121
Total	98	138	236	Total	75	161	236

Cutoff	Positive	Negative	Term/Post-term (females)		Positive	Negative	Total
			Total	Cutoff			
≤ 32 (+)	143	66	209	≤ 31.5 (+)	102	26	128
> 32 (-)	2	152	154	> 31.5 (-)	11	224	235
Total	145	218	363	Total	113	250	363

Preterm			
Cutoff	Positive	Negative	Total
≤ 30 (+)	24	14	38
> 30 (-)	0	47	47
Total	24	61	85

Discussion

Using the Brazilian Ministry of Health criterion (HC ≤ 33cm), classification of the Fenton curves for the 684 newborns reported as suspected cases of microcephaly shows 417 false-positives (61%).

Meanwhile, analysis of the ROC curves using Fenton as the gold standard points to a cutoff point of 32cm for HC in both sexes, consistent with the new recommendation by the Ministry of Health⁸.

Lowering the cutoff point for HC from 33cm to 32cm increased the accuracy of the case definition for microcephaly, by sex and GA, according to the Fenton method. Among term/post-term neonates of both sexes, the number of false-positives fell from 275 (45.9%) to 94 (15.7%).

Still, the adoption of a single cutoff point (32cm) for both sexes does not appear appropriate⁹, since it results in a 10% drop in specificity for female term and post-term neonates, producing more false-positives in the latter group. This finding explains the large volume of reported suspected cases of microcephaly in females, despite the lack of a significant difference between the sexes in the proportion of positive cases.

Considering preterm neonates, a cutoff of 30cm produced 14 false-positives among the 85 suspected cases.

Since it shows higher specificity, the Intergrowth method pointed to HC = 31.5cm as the cutoff that produces the largest area under the ROC curve for males, compared to 31cm for females. However, since screening requires greater sensitivity than specificity, the choice would be 32cm for males and 31.5cm for females. Importantly, variation in HC measurements is possible in this epidemic, due to phenotypical characteristics such as excess scalp skin as a result of cerebral atrophy¹⁰. The cutoff for HC in newborns should be sensitive enough to generate an excessive number of notifications. Adoption of the third percentile for the curves from the two methods as the classification criterion would mean reporting 3% of the term birth cohort as suspected cases of microcephaly¹¹. Meanwhile, the recommendation of lower cutoff points, that is, more specific and which would include lower percentages of births for investigation, might exclude cases that would warrant investigation to identify possible abnormalities.

In conclusion, critical and on-going analysis is necessary to support surveillance of microcephaly cases in newborns in the context of the current epidemic. Other clinical and/or phenotypical criteria should be explored, as well as findings from imaging tests, in order to establish a more accurate gold standard and improve the

reporting, investigation, and treatment of cases. These aspects are crucial for improving knowl-

edge of this new syndrome, probably associated with the Zika virus infection.

Contributors

W. V. Souza, T. V. B. Araújo, and M. F. P. M. Albuquerque contributed to the conception, analysis, and writing of the article. M. C. Braga collaborated in the writing and revision. R. A. A. Ximenes participated in the conception, analysis, and revision. D. B. Miranda Filho collaborated in the conception and revision. L. C. A. Bezerra, G. S. Dimech, P. I. Carvalho, R. S. Assunção, R. H. Santos, and W. K. Oliveira contributed to the discussion and revision. L. C. Rodrigues and C. M. T. Martelli participated in the conception, analysis, and revision.

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Resumo

O aumento das notificações de casos de microcefalia em Pernambuco, Brasil, e no Nordeste caracterizou uma epidemia que levou o Ministério da Saúde a decretar emergência nacional de saúde pública. Inicialmente, o Ministério da Saúde definiu como suspeitos recém-nascidos de 37 semanas ou mais de idade gestacional (IG) e com perímetro cefálico (PC) ≤ 33 cm, tendo, em dezembro de 2015, reduzido essa medida para 32cm. Este estudo objetivou estimar a acurácia, a sensibilidade e a especificidade de diferentes pontos de corte para o PC, utilizando curvas ROC e, como padrões-ouro, as curvas de Fenton e de Intergrowth 2014. Foram descritos os casos notificados em Pernambuco entre 2 de agosto de 2015 e 28 de novembro de 2015, segundo sexo e categorias de IG. Os métodos de Fenton e de Intergrowth fornecem curvas de crescimento para o PC de acordo com IG e sexo, considerando positivos para microcefalia os recém-nascidos com PC abaixo do percentil 3 dessas distribuições. Dos 684 casos notificados, 599 foram recém-nascidos a termo/pós-termo. Para esses, as análises com curvas ROC mostram, segundo Fenton, que o ponto de corte que apresentou maior área sob a curva ROC, com sensibilidade maior que especificidade, foi 32cm, para ambos os sexos. Pelo método de Intergrowth, os pontos de corte, respeitando os mesmos critérios, são 32cm e 31,5cm, para os sexos masculino e feminino respectivamente. O ponto de corte identificado, segundo Fenton (32cm), coincidiu com a recomendação do Ministério da Saúde. Adotando-se Intergrowth como padrão, a escolha seria de 32cm, para o sexo masculino, e de 31,5cm, para o sexo feminino. Concluindo, aponta-se a necessidade de realizar análises críticas e continuadas para avaliar pontos de corte, incluindo outras características para a definição de caso.

Microcefalia; Infecção por Zika Vírus; Vigilância Epidemiológica; Confiabilidade dos Dados

Resumen

El aumento de las notificaciones de casos de microcefalia en Pernambuco, Brasil, y en el Nordeste caracterizó una epidemia que condujo al Ministerio de Salud a decretar una emergencia nacional de salud pública. En un primer momento, el Ministerio de Salud definió como casos sospechosos a recién nacidos de 37 semanas o más de edad gestacional (IG) y con perímetro cefálico (PC) ≤ 33 cm, siendo, en diciembre de 2015, reducida esa medida a 32cm. Este estudio tuvo por objetivo estimar la precisión, sensibilidad y especificidad de diferentes puntos de corte para el PC, utilizando curvas ROC y, como patrones oro, las curvas de Fenton y de Intergrowth (2014). Se describieron los casos notificados en Pernambuco entre 2/Agosto/2015 y 28/Noviembre/2015, según sexo y categorías de IG. Los métodos de Fenton y de Intergrowth proporcionan curvas de crecimiento para el PC, de acuerdo con IG y sexo, considerando positivos para microcefalia los recién nacidos con un PC debajo del percentil 3 de estas distribuciones. De los 684 casos notificados, 599 fueron recién nacidos a término/pos-término. Para estos, los análisis con curvas ROC muestran, según Fenton, que el punto de corte que presentó una mayor área bajo la curva ROC, con sensibilidad mayor que especificidad, fue 32 cm, para ambos sexos. Por el método de Intergrowth los puntos de corte, respetando los mismos criterios, son 32cm y 31,5cm para los sexos masculino y femenino, respectivamente. El punto de corte identificado, según Fenton (32cm), coincidió con la recomendación del Ministerio de Salud. Adoptándose Intergrowth como patrón, la elección sería 32cm para el sexo masculino y 31,5cm para el sexo femenino. Como conclusión, se apunta la necesidad de realizar análisis críticos y continuados para evaluar puntos de corte, incluyendo otras características para definición de caso.

Microcefalia; Infeción por el Virus Zika; Vigilancia Epidemiológica; Exactitud de los Datos

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