The challenge of assessing microcephaly in the context of the Zika virus epidemic

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Abstract

The present report examines the impact of the current limitations of the microcephaly definition in the context of the Zika virus outbreak. It highlights its dependence on the method used for determining gestational age and other anthropometric parameters, and includes original results of prevalence of microcephaly in four countries from two different continents (Mozambique, Brazil, Guatemala and Colombia). Alternative definitions of microcephaly are proposed in order to allow the identification of true cases of microcephaly in a more accurate manner.

The epidemic of Zika virus (ZIKV) is steadily spreading in the Americas, as well as in some African and Asian countries. Although most infections seem to be asymptomatic or with a mild clinical presentation, ZIKV infection during pregnancy has been associated with severe fetal outcomes, including microcephaly (1). The WHO has recommended reporting the prevalence of microcephaly as part of the ZIKV surveillance in countries at risk or with ongoing transmission.

Microcephaly is a neurological condition in which the head circumference (HC) is smaller than expected in a baby of the same gestational age (GA) and sex. It is estimated to occur in 1 per 6200-8500 births and it may be associated with mental retardation (2).

Different HC cut-off values have been used for defining microcephaly. According to a recent WHO interim guidance update, microcephaly is recommended to be defined as a HC below two Standard Deviations on the reference curves, as measured in the first 24 hours of life (3). For full term newborns (37-41 weeks), it is suggested to use the WHO growth curves, by sex (that is, a cut off of 31.5 cm and 31.9 cm for girls and boys respectively) (4). Intergrowth-21 Size at Birth Standards (5) are preferred for premature and post term newborns or when accurate gestational age is known. Currently, international recommendations for identifying cases of microcephaly warn of the importance of accuracy in determining gestational age and proportionality of HC to body size (3), which are two issues not taken into account in the previous various definitions of microcephaly used.

However, these warnings do not materialize into concrete and objective measures and, therefore, neonates that need special management and follow-up should be identified only by the experience and subjectivity of the health professionals providing care to neonates and their families.

Several methods can be used to estimate gestational age, such as the date of last menstrual period (LMP), ultrasound (US), or clinical assessment. Postnatal examination of the newborn with clinical scoring for external and/or neurological characteristics, such as the Dubowitz test (6) or Ballard score (7), are used in low-income countries where LMP estimates are usually unreliable, attendance in early pregnancy for prenatal care is unusual and ultrasound examination is rarely available. The agreement between these methods has not been well established. It has been observed that Dubowitz score underestimates GA in small-for gestational-age (SGA) and term infants (8). In addition, Ballard exam misclassified approximately 80% of preterm infants as term when compared with the best obstetric estimate combining LMP with US, suggesting an overestimation of GA (9).

A small head is not strictly synonymous with microcephaly. It could be the result of intrauterine growth retardation as it happens in SGA babies, or simply be due to a genetic family condition (10). The disproportionality between the cranial dimension and body size is omitted in the definition of microcephaly. Few studies have investigated the association between HC and other anthropometric measures, such as weight and height, with widely variable and even conflicting results (11). Cubed HC and body weight significantly correlate, giving an almost constant average of 10 cm^3/g and standard deviation of 1, and this seems to be a useful

index to assess the proportion of head size to body mass at birth and during infancy (12). The measurement of this index could contribute to early diagnosis of diseases such as hydrocephalus or microcephaly (12).

To illustrate this discussion and provide baseline data for surveillance, we have calculated the prevalence of microcephaly in babies born to mothers enrolled in two different pregnancy cohort studies among Mozambican women (13, 14, 15), where Dubowitz and Ballard tests were used to determine the GA; and in another study carried out in three Latin American countries (Guatemala, Brazil and Colombia) (16), in which the Ballard score or ultrasound were used. Results of the estimated prevalence of microcephaly in 4730 newborns of 26-42 weeks of gestational age with complete information of anthropometric measurements at birth are shown in Table 1.

The prevalences of microcephaly defined according to WHO guidelines were 1.7% and 4.1% in Mozambique; and 8.2%, 12.5% and 15.2% in Brazil, Colombia and Guatemala respectively (Table 1). The difference in prevalence between the two studies in Mozambique could be explained by the different methods used for GA estimation. Of the total 327 cases of microcephaly, 169 were SGA (52%) and they had a mean ratio of HC relative to body mass of 12.2 cm3/g [95%CI: (11.9, 12.6)], which is above the reference average of 10 cm3/g. This suggests that their heads were not smaller than expected for their body size, but they were either babies with growth retardation, or there was an overestimation of their GA. In contrast, the corresponding mean ratio among newborns with microcephaly who were not SGA was 10.0 cm3/g [95%CI: (9.8, 10.2)], which means that some of them may

truly have a smaller than expected head. Consequently, we calculated the prevalence of microcephaly among babies not SGA (central column of Table 1), obtaining a much lower proportion of microcephaly. The values obtained with this definition should be closer to reality since it incorporates the concept of disproportionality of HC to body size taking into account whether the newborn is SGA or not. This is one explicit recommendation of the WHO guidelines, but no objective measure is proposed for it, and SGA could be one of them. However, this definition does not allow to identify microcephaly among SGA newborns. Thus, in order to assess the prevalence of microcephaly including those with SGA, we propose an alternative definition (third column of Table 1) that takes into account the ratio of HC to body weight. The main advantage of using this ratio is that it does not depend on the method used for GA assessment, all of which have important limitations in low and middle-income settings. Thus, it could widely be used in these settings for individual case management and microcephaly surveillance in a more accurate manner.

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Table 1. Prevalence of Microcephaly and 95% Confidence Interval at different sites and methods for GA assessment

Site	Gestational age [a]	Microcephaly [b]	Microcephaly [b] & not SGA [c]	Microcephaly [b] & disproportionality [d]
Mozambique [e]	Prematures	5/41 [12.2%; (4.1, 26.2)]	0/41 [0.0%; (0.0, 8.6)]	0/41 [0.0%; (0.0, 8.6)]
	Full term	10/795 [1.3%; (0.6, 2.3)]	0/795 [0.0%; (0.0, 0.5)]	1/795 [0.1%; (0.0, 0.7)]
	Post term	1/104 [1.0%; (0.0, 5.2)]	0/104 [0.0%; (0.0, 3.5)]	0/104 [0.0%; (0.0, 3.5)]
	Overall	**16/940 [1.7%; (1.0, 2.7)]**	**0/940 [0.0%; (0.0, 0.4)]**	**1/940 [0.1%; (0.0, 0.6)]**
Mozambique [f]	Prematures	11/165 [6.7%; (3.4, 11.6)]	3/165 [1.8%; (0.4, 5.2)]	0/165 [0.0%; (0.0, 2.2)]
	Full term	65/1680 [3.9%; (3.0, 4.9)]	38/1680 [2.3%; (1.6, 3.1)]	15/1680 [0.9%; (0.5, 1.5)]
	Post term	0/26 [0.0%; (0.0, 13.2)]	0/26 [0.0%; (0.0, 13.2)]	0/26 [0.0%; (0.0, 13.2)]
	Overall	**76/1871 [4.1%; (3.2, 5.1)]**	**41/1871 [2.2%; (1.6, 3.0)]**	**15/1871 [0.8%; (0.4, 1.3)]**
Brazil [f]	Prematures	5/27 [18.5%; (6.3, 38.1)]	2/27 [7.4%; (0.9, 24.3)]	0/27 [0.0%; (0.0, 12.8)]
	Full term	52/653 [8.0%; (6.0, 10.3)]	27/653 [4.1%; (2.7, 6.0)]	17/653 [2.6%; (1.5, 4.1)]
	Post term	2/37 [5.4%; (0.7, 18.2)]	2/37 [5.4%; (0.7, 18.2)]	2/37 [5.4%; (0.7, 18.2)]
	Overall	**59/717 [8.2%; (6.3, 10.5)]**	**31/717 [4.3%; (3.0, 6.1)]**	**19/717 [2.6%; (1.6, 4.1)]**
Colombia [g]	Prematures	1/33 [3.0%; (0.1, 15.8)]	0/33 [0.0%; (0.0, 10.6)]	0/33 [0.0%; (0.0, 10.6)]
	Full term	23/187 [12.3%; (8.0, 17.9)]	19/187 [10.2%; (6.2, 15.4)]	10/187 [5.3%; (2.6, 9.6)]
	Post term	8/35 [22.9%; (10.4, 40.1)]	6/35 [17.1%; (6.6, 33.6)]	7/35 [20.0%; (8.4, 36.9)]
	Overall	**32/255 [12.5%; (8.7, 17.3)]**	**25/255 [9.8%; (6.4, 14.1)]**	**17/255 [6.7%; (3.9, 10.5)]**
Guatemala [f]	Prematures	2/42 [4.8%; (0.6, 16.2)]	2/42 [4.8%; (0.6, 16.2)]	1/42 [2.4%; (0.1, 12.6)]
	Full term	48/592 [8.1%; (6.0, 10.6)]	29/592 [4.9%; (3.3, 7.0)]	14/592 [2.4%; (1.3, 3.9)]
	Post term	94/313 [30.0%; (25.0, 35.4)]	30/313 [9.6%; (6.6, 13.4)]	20/313 [6.4%; (3.9, 9.7)]
	Overall	**144/947 [15.2%; (13.0, 17.7)]**	**61/947 [6.4%; (5.0, 8.2)]**	**35/947 [3.7%; (2.6, 5.1)]**

(a): Prematures (born before 37 weeks of pregnancy), full term (37 to 41 weeks), or post term (more than 41 weeks of pregnancy)
(b): Defined according to the WHO Child Growth Standards for full term neonates from Mozambique, Brazil and Guatemala (not accurate gestational age); Intergrowth-21 Size at Birth Standards were used for full term neonates from Colombia (gestational age determined by US) and for all prematures and post term neonates
(c): Defined as having a birth weight less than the 10th percentile for the gestational age according the Intergrowth-21 Size at Birth Standards
(d):$(HC(cm)^3/\text{Body weight}(g)) < 10$
(e): Gestational age by Dubowitz test
(f): Gestational age by Ballard score
(g): Gestational age by Ultrasound