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Congenital microcephaly: A diagnostic challenge during Zika epidemics

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ABSTRACT

The multiple, wide and diverse etiologies of congenital microcephaly are complex and multifactorial. Recent advances in genetic testing have improved understanding of novel genetic causes of congenital microcephaly. The recent Zika virus (ZIKV) epidemic in Latin America has highlighted the need for a better understanding of the underlying pathological mechanisms of microcephaly including both infectious and non-infectious causes. The diagnostic approach to microcephaly needs to include potential infectious and genetic etiologies, as well as environmental *in-utero* exposures such as alcohol, toxins, and medications. Emerging genetic alterations linked to microcephaly include abnormal mitotic microtubule spindle structure and abnormal function of centrosomes. We discuss the diagnostic challenge of congenital microcephaly in the context of understanding the links with ZIKV emergence as a new etiological factor involved in this birth defect.

1. Introduction

As of February 2018, ZIKV infections had been documented in 85 countries and territories, 49 of which are in the Americas, including Brazil, Colombia, Mexico, Guatemala, Honduras, El Salvador, Panama, Dominican Republic, Puerto Rico, Guadeloupe, Barbados, Ecuador, Venezuela, Surinam, Guyana, French Guyana, Bolivia, Paraguay, Costa Rica, Nicaragua and Peru [1]. To fully understand the impact of this emerging pathogen in the pediatric population, a comprehensive understanding on other causes of primary microcephaly affecting neonates (infectious and non-infectious) is highly relevant.

Although strong epidemiological evidence suggests viral circulation of Zika virus (ZIKV) in Brazil since 2013 [2], the onset to epidemic proportions of cases in Latin America since 2015 has triggered concerns due to a simultaneous increase in the reporting of congenital microcephaly cases.

It is clear now that this arboviral infection has been associated with an increased incidence of microcephaly in fetuses born to infected mothers [3]. Specifically, an increase in reported cases of congenital microcephaly observed during the last months of 2015 in Brazil have raised concerns in neighboring countries known to have circulation of this mosquito-borne pathogen.

The following paper will discuss a clinical approach to microcephaly in the Americas, with an emphasis on the diagnostic process for infectious etiologies from the clinician's perspective in the context of the emergence of congenital Zika virus syndrome.

1.1. Defining microcephaly

A measurement of head circumference (HC) (also called occipitofrontal circumference [OFC]), is determined by placing a measuring tape (with cm and mm scale) around the head to include the widest part of the forehead and the most prominent part of the occipital area to arrive at the largest possible measurement. According to this,

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Fig. 1. Cases of microcephaly of Colombia (photos taken by Jorge L. Alvarado-Socarras).

microcephaly is defined as a head size that is 2 standard deviations (SD) below the mean, based on age and sex, according WHO guidelines. Alternatively, Barkovich defines OFC as more than 3 SDs below the mean [4] (Figs. 1 and 2). If we are to follow the first definition mentioned above, 2.3% of neonates in the Americas would fall in the range as microcephalic where as severe microcephaly (considered as an OFC $\leq$3 SD at birth) would be expected in up to 0.1% of children assuming a normal distribution, which agrees with the published estimate of 0.14% of neonates [5]. WHO defines microcephaly as a HC below 2 standard deviations on the reference curves measured within the first 24 life hours. But, for full term neonates (> 37 weeks) the cut-off value is 31.5 cm and 31.9 cm for girls and boys respectively [6]. The definition of microcephaly (Figs. 1 and 2) used becomes particularly relevant considering that a value below the cut-off does not necessarily imply evidence of clinical neurologic or developmental impairment but may simply represent the low end of the population distribution. However, other factors can be adjusted and taken into consideration in these definitions, as for example the prematurity and parental head circumference [7]. In general, severity is related to prognosis.

1.2. Potential pitfalls in the measurement of head circumference

Measurement of the HC is an important parameter in the pediatric population and a series of measurements over time are generally regarded as more instructive than a single measurement. However, there are pitfalls in the interpretation of abnormal head circumference at birth [8]. The measured size of the head in comparison with age-related norms is used to determine the definition of macrocephaly or microcephaly and this is used as a preliminary screen for conditions associated with neurologic impairment. Nevertheless, the major issue now is how to define microcephaly when more than one criterion and reference patterns would be applicable in different populations and clinical scenarios [8].

Microcephaly is a clinical and anthropometrical sign, which can potentially signal an abnormality in brain growth and development with a reported incidence ranging from 1:6200 to 1:8500 [8]. However, it's true incidence may be confounded by differences in measurement and reporting, varying in different geographical settings [9].

1.3. Classification of microcephaly

Several classifications of microcephaly have been adopted over time. Microcephaly can be considered isolated, or in association with other anomalies, (chromosomal or syndromic conditions), linked to other growth parameters (symmetric or asymmetric) or distinct etiologic determinants (genetic or environmental) [10,11]. The most frequently used classification relies on the timing of onset. Congenital microcephaly (also defined as primary microcephaly), is present at birth or by 36 weeks' gestation [9]. These terms do not imply a distinct etiology and can be seen with either genetic or environmental causes of neurodevelopmental impairment [12]. Secondary microcephaly refers to a failure of normal brain growth and change in measured head circumference after birth [10] and is usually due to a subsequent loss of dendritic connections [13]. Also, microcephaly has been traditionally categorized based on Giacomino's classification as: (1) Microcephalia Vera, where brain size remains small without any sign of injury or deformation; (2) Microcephalia Aspuria, in which some pathological changes and injury to the brain can be observed, and (3) Microcephalia Combinata, where a small brain size with evidence of injury are observed [14].

Neuroanatomic abnormalities frequently associated with microcephaly include holoprosencephaly, atelencephaly, lissencephaly, schizencephaly, polymicrogyria, macrogyria, and fetal brain disruption sequence [15,16]. It is important to mention that in microcephaly, although the brain is usually very small, -usually 3 standard deviations below the mean-its architecture can remain grossly normal with no link to other systemic anomalies. In addition, pregnancy, delivery and the postnatal period usually follow an uneventful course. Affected patients almost always have mental retardation but an otherwise unremarkable neurologic examination. A sloping forehead and prominent ears are usually the classic dysmorphic features seen in these cases.

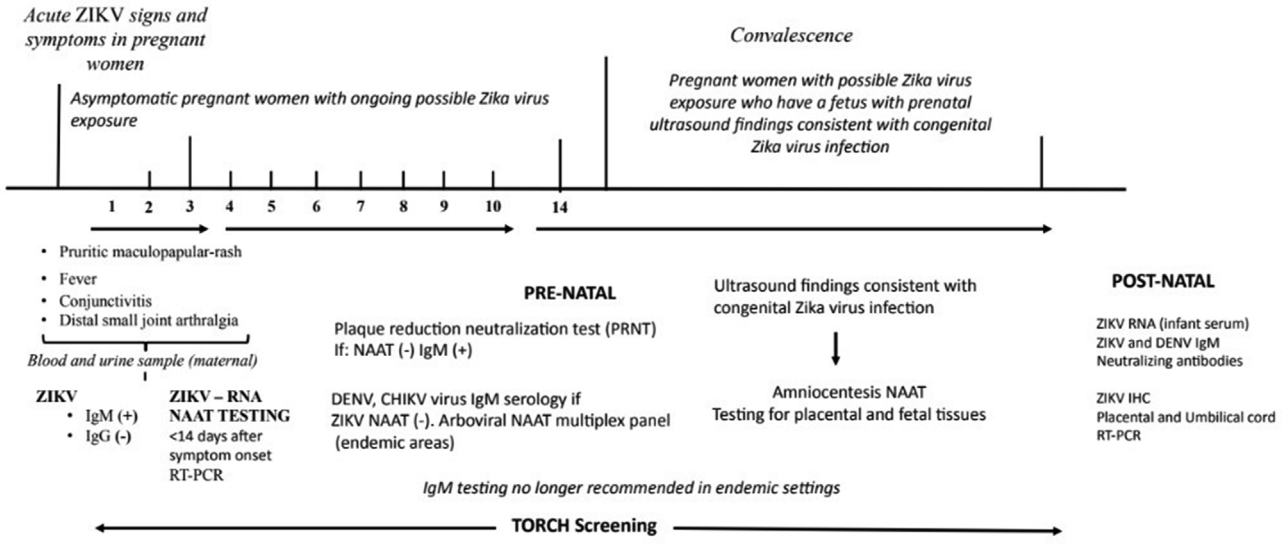

Fig. 2. Timeline: diagnostics of microcephaly.