MICROCEPHALY

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Abstract

Microcephaly is a condition in which the size of the head is smaller than expected for gestational age. Microcephaly can be an isolated condition, or it can occur in combination with other major birth defects; researchers are studying the link between Zika virus infection and microcephaly.

Rezumat: Microcefalia

Microcefalia este o afecţiune în care dimensiunea capului este mai mică decât era de aşteptat pentru vârsta gestaţională. Microcefalia poate fi o condiie izolată, sau poate să apară in combinaţie cu alte defecte congenitale majore; cercetatorii studiază legătura dintre infecţia cu virusul Zika şi microcefalie.

Cuvinte cheie: microcefalie, virusul Zika, diagnostic prenatal

Introduction

Microcephaly refers to the presence of an abnormally small head for gestational age and is usually indicative of an underlying problem with brain development (1), but the definition of microcephaly after birth is not uniform. Usually it is defined as an occipitofrontal circumference (OFC) more than 2 standard deviations (SD) below the mean for age and gender, but some authors put the OFC cut-off at –3SD (2).

The most reliable way to assess whether a baby has microcephaly is to measure head circumference 24 hours after birth, compare the value with WHO growth standards, and continue to measure the rate of head growth in early infancy (3).

Postnatally, the risk for developmental disabilities for microcephaly is 11% when head circumference is -2SD, 50-75% in -3SD and 100% when head circumference is smaller than -4SD (4).

This review addresses our current understanding of newborn microcephaly: causes, prenatal diagnosis and treatment.

Incidence

Microcephaly is a rare condition. Reported estimate incidence of microcephaly has wide variation due to the differences in the definition and target population (3).

Causes of microcephaly

Microcephaly can result from chromosomal abnormalities, exposure to drugs, alcohol, other

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enviromental toxins, premature fusion of the bones of the skull (craniosynostosis), certain metabolic disorders and congenital infections (5).

Genetic causes

Genetic causes of neonatal microcephaly include brain malformations such as holoprosencephaly, primary microcephaly; lissencephally, or schizencephaly, neurometabolic diseases such as Smith-Lemli-Opitz disease, and chromosomal abnormalities such as trisomy 13 or 18 (6).

Five subsets of microcephaly emerged from one study: (1) isolated microcephaly (16.7%); (2) microcephaly due to holoprosencephaly (16.7%); (3) microcephaly associated with chromosomal disorders (23.3%); (4) microcephaly as part of a genetic syndrome (20.0%); and (5) microcephaly as part of multiple anomalies (23.3%) (7).

Acquired microcephaly

Microcephaly related to Zika virus infection

The World Health Organization (WHO), in a document published in November 2015, warns that urbanization and globalization are potential risks for outbreaks of infection with Zika virus anywhere in the world where the vector is present or may be established in the future (8).

The explanation for what caused this virus, previously confined to a zoonotic niche in Africa, to become a major pandemic threat is as yet unknown but three factors are thought to play a significant role. The increase in Aedes aegypti infestations is an important factor and the spread of Aedes albopictus may play a role. The pandemic strain of Zika differs significantly from the African strain. Codon usage by the pandemic strain is optimized for replication in human cells. Another major factor is immune enhancement by pre-existing heterologous anti-flavivirus antibodies (9)

The ZIKV natural transmission cycle involves mosquitoes, especially Aedes spp, but perinatal transmission and potential risk for transfusion-transmitted ZIKV infections has also been demonstrated (10).

At present, Zika virus testing for the assessment of risk for sexual transmission is of uncertain value, because current understanding of the duration and pattern of shedding of Zika virus in the male and female genitourinary tract is limited. Therefore, testing of specimens to assess risk for sexual transmission is currently not recommended (11).

The complication we are most concerned about now, however, is mother-to-child transmission. (12). The risk of microcephaly or congenital abnormalities in newborns associated with ZIKV is greater when the infection occurs in the first trimester of pregnancy.

Discussion of the advantages and risks of an amniocentesis for ZIKV RT-PCR

Pregnant women with a history of travel to an area with Zika virus transmission and who report two or more symptoms of Zika virus disease (acute onset of fever, maculopapular rash, arthralgia, or conjunctivitis) during or within 2 weeks of travel, or who have ultrasound findings of fetal microcephaly or intracranial calcifications, should be tested for Zika virus infection (13).

The mother should be made aware that the sensitivity and specificity of this test for detecting congenital infection are unknown and that the likelihood of the fetus being affected is also unknown. However, in the case of a fetal brain abnormality on ultrasound and a positive ZIKV RT-PCR result, the likelihood of the two being associated is high (14).

As of March 2016, definitive diagnosis of Zika virus is made by RT-PCR testing of blood and saliva, which can only be accomplished with assistance from public health authorities and is not yet available at individual hospitals. Results are generally not accessible in a timely fashion (15).

In fact, there is an urgent necessity to develop rapid tests (immunochromatographic), serological (IgM- and IgG-ELISA) and molecular tests for the early diagnosis of ZIKV infection, especially for the most vulnerable groups, i.e., pregnant women and individuals with autoimmune conditions and chronic diseases (16).

With proven or suspected microcephaly, testing for other etiological factors is important, including rubella, cytomegalovirus (CMV), toxoplasmosis, herpes simplex virus, varicella zoster virus, HIV, and chikungunya virus, as well as excluding other noninfectious causes (17).

Treatment options

Unfortunately, there is currently no vaccine to prevent or treatment to cure Zika infection (1).

HIV infection

HIV is a neurotrophic virus and causes devastating neurological insults to the immature brain. Acquired microcephaly due to impaired brain growth is a feature often encountered in children with progressive types of HIV-related encephalopathy (18).

The majority of children with HIV-associated neurological disease are infected by maternal–fetal transmission. Through this route, there is an increased risk of irreversible brain damage, including cerebral atrophy, intracerebral calcifications, and microcephaly, as well as various degrees of developmental delay and cognitive impairment (19).

A recent study has been reported that: HIV-infected children had lower head circumferences and more microcephaly than HIV-uninfected children. Timing of HIV acquisition; influenced HCZ (head circumference-for-age Z-scores). Correlations between head growth and neurodevelopment in the context of maternal/infant HIV infection, and further studies from the current ART era, will help determine the predictive value of routine head circumference measurement (20).

Diagnosis

Microcephaly proved to be part of a complex problem, emphasizing the need of a meticulous search for structural anomalies and fetal karyotyping when biometric data are not according to gestational age (7).

The in utero measurement of the head circumference is more precisely a measurement of the skull and as such is equivalent to the clinical measurement of the head circumference after birth (21). Although HC measures skull size, it typically also reflects overall brain volume and has been described as a "widely used proxy of neural growth and brain size" (22).

Unlike ventriculomegaly, for which there is consensus on its prenatal definition, there is no absolute threshold for the definition of prenatal microcephaly; the smaller the head dimension, the greater the probability of microcephaly with underlying pathology. A major increase in pericerebral space associated with a decrease in cephalic biometry indicates and reinforces the severity of the microcephaly. A moderate, isolated and non-progressive decrease in cephalic biometry is, in most cases, associated with favorable outcome when the appropriate biological work-up (including cytogenetic and infectious testing) is also negative (23).

Leibovitz et al. have proposed to improve prenatal diagnosis of microcephaly using three reference ranges for fetal head circumference. The study showed no significant improvement in predicting microcephaly at birth by application of new HC references in comparison with an established reference (2).

It should be noted that preimplantation genetic diagnosis is also potentially available whenever the chromosomal or gene defect is known. However, if no gene defect is discovered, these studies cannot be done, and the only option for prenatal diagnosis would be serial ultrasound studies, which may be helpful for syndromic forms but not for isolated microcephaly, because slow head growth may not be obvious until relatively late in pregnancy (24).

Physicians today have two alternatives: either use the 3SD cutoff as recommended by Chervenak et al. and endorsed by the Society for Maternal-Fetal Medicine (SMFM) or develop a new dataset for one's population with statistical validation (25).

Treatment and care

There is no specific treatment for microcephaly (3). Since each child develops complications that differ in type and severity, which may include respiratory, neurological and motor

problems, the follow-up by different specialists will depend on which functions have been compromised (26).

Discussion

Microcephaly can be divided into primary (or true) or secondary microcephaly. In primary microcephaly the brain never forms normally whereas in secondary microcephaly normal continued brain development is arrested by some defined insult / event. The terms congenital and acquired can also be used which only partially overlap with primary and secondary (27).

Prenatal diagnosis of microcephaly is based on a comparison of the biometric parameters obtained during monitoring of dynamic fetal ultrasound and becomes easier as the gestation advances. Therefore, at least one ultrasound should be done after 28 weeks' gestation. In addition the diagnosis should be reserved for cases where there is a significant discrepancy between the head size and the rest of the body (27). Measurement of the biparietal diameter is not helpful in the diagnosis of microcephaly, but can help in revealing skull shape abnormalities (21)

Medical and genetic counseling of families with children with microcephaly is needed to assess the potential risk in subsequent pregnancies.

CONCLUSION

Microcephaly is a progressive condition and prenatal diagnosis is impossible in most cases. The available experience suggests that even expert ultrasound in pregnancies at risk will fail to diagnose fetal microcephaly in many cases (28*)*. SMFM recommend that isolated fetal microcephaly should be defined as fetal HC e"3SD below the mean for gestational age. The diagnosis of pathologic microcephaly is considered certain when the fetal HC is e"5SD. A detailed neurosonographic examination should be performed and follow-up ultrasound done in 3-4 weeks (29).

On 18 November the World Health Organization declared that Zika virus was no longer a public health emergency of international concern but was still a "significant and enduring health challenge" (30).

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