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SPECIAL ARTICLE

Microcephaly: Significance and how to approach during the zika era

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ABSTRACT

Microcephaly is an uncommon but important ultrasonographic finding. The smallest-head infants trend to suffer the severest level of developmental delay. Currently, more than three SDs below the mean is accepted as the definition for microcephaly diagnosis. Wrong gestational age determination, craniosynostosis and intrauterine growth restriction (IUGR) are firstly differentiated. Then, associated abnormalities and pathognomonic clues for diagnosing the etiologic cause of microcephaly should be ultrasonographically surveyed. Teratogenic exposure, intrauterine infection (TORCH and zika) and genetic abnormalities are possible etiologies. Prognosis and management depend on gestational age, severity of head size, associated anomalies and possible cause.

Keywords: microcephaly, zika, TORCHS

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The term "fetal microcephaly" is used for defining fetus whose head size is smaller than is appropriate for their gestational age. Head size is usually correlative to brain size, especially forebrain[1]. Thus, the postnatal intellectual disability, degree of severity and neurological delay associated with microcephaly depends on the size of the fetal head[2]. Infants with the smallest heads tend to suffer the severest levels of developmental delay.

Since the beginning of the 2014 worldwide zika epidemic, the zika virus was worldwide alerted and has been reported in travelers returning from Southeast Asia including Thailand[3,4]. The zika virus can cross the placenta and cause microcephaly in the fetus, with the greatest risk in early pregnancy[5]. So, Thai obstetricians should be familiar with microcephaly and how to approach it.

Incidence

The incidence of neonatal microcephaly was reported around 1.3 to 150 per 100,000 live births. The true prenatal incidence was unknown but it is thought to be higher than in the neonatal period because some cases probably die intrauterine or stillborn[6-7].

Diagnosis

Standard biometric head circumference (HC) is commonly measured for microcephaly diagnosis. However, the definite quantitative cut-off is still controversial[6, 8-11]. If a fetal HC is more than 2 or 3 standard deviations below the mean (mean -2 or 3 SD), an abnormality is suspected. Importantly, most fetuses with HC level less than mean – 2SD (about 2.5% of normal general population) will have normal neurological development and intelligence[12]. So family anxiety is concern if microcephaly is diagnosed using this cut-off. Finally, more than three SDs below the mean defines as microcephaly. This cut off is consistent with epidemiological incidence of microcephaly (0.1% of the overall population)[10] and is intended to identify infants at risk of abnormal neurological development. The mean and deviated values of HC according to gestational age are previously reported[13].

Differential diagnosis

Craniosynostosis and intrauterine growth restriction (IUGR) caused by severe placental insufficiency are common conditions that affect the HC value. An abnormal cranial shape is an important clue for craniosynostosis. A normal cranial shape with or without sloping forehead is consistent to microcephaly. For IUGR, decreased amniotic fluid amount, small abdominal circumference (AC) and abnormal Doppler indices may be present. Interestingly, measurements of the transverse cerebellar diameter (TCD) to the caval-calvarial diameter (CCD) ratio (Fig. 1.) is an adjunctive parameter to identify pathological microcephaly and TCD/CCD ratio greater than the 90th percentile suspect for microcephaly[14].

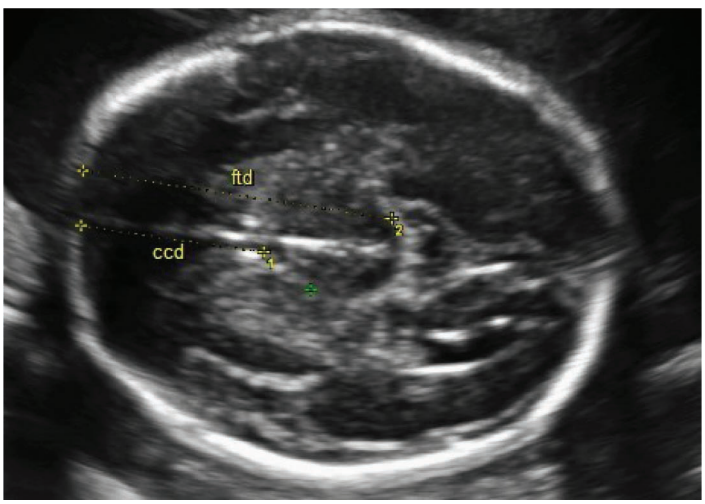

Fig. 1. Axial ultrasonographic image presented of caval-calvarial distance (ccd) and frontothalamic distance (ftd).

How to approach microcephaly during the zika era

1. Accurate gestational age is an important aspect that should be documented before microcephaly diagnosis. Menstrual history, contraceptive methods, quickening time, uterine size and earliest ultrasonography must be assessed to determine the gestational age. Then a complete ultrasonographic structural scan should be performed to identify the associated abnormality and reveal pathognomonic clues for diagnosis the etiologic cause of microcephaly such as holoprosencephaly in chromosomal aberration, porencephaly in destructive brain lesion, cranial sign (lemon-shaped head and banana cerebellum) in spina bifida, intracranial calcification in intrauterine infection, etc.

2. Interview the patient to find any history of teratogenic exposure, risk of chromosomal aberration, chromosomal aberration risk assessment, previous

intrauterine infection or risk of infection exposure including TORCHS and zika infection. Clinical presentation of TORCHS infection mostly asymptomatic and non-specific. For zika infection, common presentations are mild fever, arthralgia, myalgia, headache, cutaneous maculopapular rash, conjunctivitis and retro-orbital pain[15]. Alcohol, cocaine, radiation and antiepileptic drug such as carbamazepine, phenytoin, barbiturates, sodium valproate are possible teratogenic causes of microcephaly[7].

3. The investigations depend on the suspected etiologic cause. In cases when an associated anomaly is present, karyotyping may be needed. Amniocentesis or fetal cord blood sampling is indicated in certain cases. For isolated microcephaly, investigation for intrauterine TORCHS (toxoplasmosis, rubella, cytomegalovirus, herpes simplex and syphilis) and zika infection should be checked. The zika RNA virus can be detected in maternal serum, maternal urine and amniotic fluid during the acute phase of infection (about 1 week) using reverse transcription PCR (RT-PCR)[16]. Amniocentesis-related complication must be discussed with the pregnant woman. In case of a microcephaly being revealed on ultrasonography accompanied with a positive ZIKV RT-PCR result, the likelihood of microcephaly caused by zika is high[17]. Serologic tests for immunoglobulin (Ig) including IgM and neutralizing antibody testing should be done on specimens collected ≥ 4 days after onset of symptoms. However, it is difficult to distinguish zika virus infection from other Flavivirus infections (dengue, yellow fever, Japanese encephalitis) because cross reactions are common with antibody testing. Moreover, samples for serologic diagnostic test should be collected in the acute phase (as early as possible) and a second sample 2 to 3 weeks after the first[15,16].

For pregnant women who have been confirmed for zika before presence of microcephaly, a maternal fetal medicine specialist should be consulted for fetal structural central nervous system surveillance. The Royal Thai College of Obstetrician and gynecologist recommends ultrasonographic structural screening starting at 18-20 weeks of gestation or as early as possible in cases which diagnosed at more than 20 weeks of gestation, followed by ultrasonography every 4 weeks until delivery[18]. To date, it has not been established whether the timing of a zika infection or the presence of maternal symptoms has an effect on the risk for fetal abnormalities. A previous case series including 19 singleton pregnancies in which clinical or laboratory finding suggested a potential zika infection found that 17/19 cases had CNS malformations and severe microcephaly was present in 73.7% of cases. Most microcephaly cases are detected in the late second or third trimester. Thus, management is difficult and still controversial. Both termination of pregnancy before presence of microcephaly and conservative management have been suggested. Reported abnormal ultrasonographic CNS findings include ventriculomegaly, intracranial calcification, cortical atrophy, brain parenchymal hyperechogenicity with increased subarachnoid space, enlarged cisternal magna and cerebellar vermis agenesis[19].

Conclusion

Microcephaly is an ultrasonographic finding, with the diagnosis based on an HC value more than three SDs below the mean. Necessary investigations depend on associated abnormalities and pathognomonic ultrasonographic findings. Teratogenic exposure, intrauterine infection (TORCHS and zika) and genetic abnormalities are possible etiologies. Prognosis and management depends on gestational age, severity of head size, associated anomalies and possible causes.

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