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Late onset microcephaly: failure of prenatal diagnosis

P. SCHWÄRZLER*†, T. HOMFRAY*, J.-P. BERNARD*‡, J. M. BLAND* and Y. VILLE*‡

**Fetal Medicine Unit and Department of Public Health Sciences, St. George's Hospital Medical School, London, UK and †Department of Obstetrics and Gynecology, University Hospital Innsbruck, Austria and ‡Department of Obstetrics and Gynecology, Paris-Ouest University, CHI Poissy-St-Germain, France*

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ABSTRACT

We present a case of recurrent primary developmental microcephaly of late onset, the prenatal diagnosis of which could not be achieved despite performing targeted serial ultrasound scans that revealed no obvious fetal abnormality. Serial scans for head measurements and detailed examination of the brain anatomy by both transabdominal and transvaginal sonography including color and power Doppler assessment revealed no obvious brain abnormality. Frontal lobe distance and thalamic frontal lobe distance at 36 weeks were on the 30th and 50th centiles, respectively. Growth velocity remained on the 50th centile up to 36 weeks; between 36 and 38 weeks measurements were between the 35th and 40th centiles. The infant was delivered by Cesarean section at 38 weeks on parental request. On examination after birth the head circumference was on the 9th centile, but the facies was that of a microcephalic child with a sloping forehead and neurologically he was severely abnormal. The adequacy of the normal reference ranges used is reviewed: the use of sex-specific growth charts at 38 weeks would have demonstrated the biparietal diameter and the head circumference to be on the 20th and 15th centiles, respectively, rather than just below the 40th centile. However, even sex-specific charts may not allow the recognition of a substantial number of affected fetuses. Copyright © 2003 ISUOG. Published by John Wiley & Sons, Ltd.

INTRODUCTION

Microcephaly is an etiologically heterogeneous group of disorders characterized by a head circumference smaller than 3 SD below the mean. Primary ('developmental') microcephaly needs to be distinguished from secondary ('destructive') microcephaly, the former being due to a primary genetically determined abnormality of brain development and the latter to an intrauterine incident such as intracranial hemorrhage or transplacental infection. Obstetricians and geneticists are not infrequently faced with the problem of advising the parents of a child with microcephaly of unknown origin on the possibility of recurrence in future pregnancies; following the birth of one affected child a recurrence rate of 10% is usually given in the absence of any definitive etiological factor. Although ultrasound can detect reliably many fetal anomalies, the accurate diagnosis of fetal microcephaly remains a challenge to the sonographer. The microcephaly may not present until late into the pregnancy and the head circumference may be difficult to measure by this stage, especially when the head is well down in the maternal pelvis.

A variety of head measurements have been recommended to make the diagnosis, based on the definition of head size > 3 SD below the mean. However, diagnostic methods assessing the entire fetal head show poor sensitivity for identifying such abnormalities[1]. Microcephaly is thought to be associated with a decreased size of the frontal fossa and a flattening of the frontal bone, and measurements of the frontal lobe have recently been suggested as a useful tool in the prenatal diagnosis of microcephaly[2,3].

We present a case of recurrent primary developmental microcephaly of late onset, the prenatal diagnosis of which was not achieved despite performing targeted serial ultrasound scans. The adequacy of the normal reference ranges used is reviewed.

CASE REPORT

The patient, gravida 3 para 2, was referred by a geneticist for a targeted ultrasound examination at 20 weeks of gestation because of a history of severe developmental microcephaly of unknown cause in the previous female child. This girl was delivered at

Correspondence to: Prof. Y. Ville, CHI Poissy-St Germain, Université Paris-ouest, 78303 Poissy cedex 03, France (e-mail: yville@wanadoo.fr)

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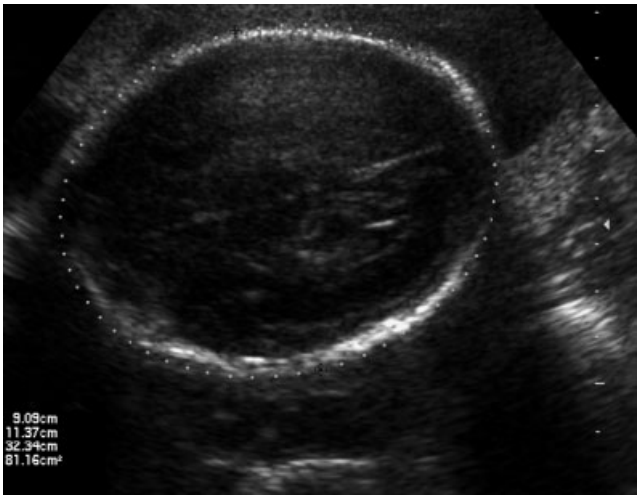

Figure 1 Transabdominal ultrasound image of the brain anatomy at 38 weeks of gestation showing no obvious brain abnormality. The head circumference was 323 mm.

Figure 2 Head circumference measurements taken in our case (○) plotted on male-specific growth chart for head circumference[6]. Measurements at 36 and 38 weeks of gestation from our case fall on the 20th and 15th centiles, respectively.

Figure 3 Head circumference measurements taken in our case (○) plotted on non-gender-specific growth chart for head circumference[6]. Measurements from our case fall on or just below the 50th centile.

term following an uncomplicated pregnancy. Routine ultrasound measurements during that pregnancy had shown a biparietal diameter on the 50th centile at 20 weeks and on the 10th centile at 34 weeks. At birth the infant was neurologically abnormal and the head circumference was just below the 4th centile. In the case presented here, a scan at 12 weeks had confirmed the gestational age calculated from the last menstrual period. An uncomplicated amniocentesis was performed at 15 weeks on parental request, and this showed a normal male karyotype. A detailed anomaly scan at 20 weeks revealed no obvious fetal abnormality and serial scans for head measurements and detailed examination of the brain anatomy by both transabdominal and transvaginal sonography suggested normal development. Growth velocity remained on the 50th centile up to 36 weeks. Between 36 and 38 weeks the head was low in the pelvis and measurements were between the 35th and 40th centiles[4]. The frontal lobe and thalamic frontal lobe distances at 36 weeks were 30 mm (30th centile) and 66 mm (50th centile), respectively[2]. Both transabdominal and transvaginal sonography of the brain anatomy including color and power Doppler[5] revealed no obvious brain abnormality (Figure 1). The use of sex-specific growth charts[6] at 38 weeks would have demonstrated the biparietal diameter and the head circumference to be on the 20th and 15th centiles, respectively (Figure 2), rather than just below the 40th centile in the non-gender-specific growth chart that we used at the time[4] as well as in that generated from our own population (Figure 3).

The infant was delivered by Cesarean section at 38 weeks on parental request due to anxiety. Examination after birth showed the head circumference to be on the 9th centile, but the facies was that of a microcephalic child with a sloping forehead. There were no other dysmorphic features. Neurologically he was severely abnormal, being extremely jittery and hypertonic.

So far the developmental progress of both infants has been similar: there has been no progress and it is difficult to assess if there has been regression. Both children suffer from recurrent epileptic seizures and severe gastroesophageal reflux, necessitating fundoplication in the girl. Magnetic resonance imaging at 7 years of age in the girl showed severe cerebral atrophy with very limited myelination but no definitive evidence of a destructive process. The microcephaly has been progressive.

DISCUSSION

lt is estimated that 20–35% of idiopathic cases of microcephaly are hereditary and problems with counseling occur when no underlying cause is diagnosed. The condition is then designated as 'true' or primary microcephaly. This is a clinical diagnosis of exclusion in an individual with a head circumference 3 SDs or more below the expected mean for that age with all discernible maternal, gestational, postnatal, chromosomal, metabolic or syndromic etiologies having been sought and eliminated. There is usually associated moderate-to-severe mental retardation. When it is familial, primary microcephaly often appears to be

transmitted as an autosomal recessive disorder, with an incidence of 1/30 000 to 1/50 000 live births[7]. A significant proportion of cases are associated with parental consanguinity and while the present case also seems to have occurred with an autosomal recessive mode of inheritance, other modes of genetic inheritance can occur[8]. Some of the genes that cause congenital microcephaly are likely to control crucial aspects of neural development and they may also be involved in the evolutionary explosion of cortical size that characterizes primates. Primary microcephaly is thought to result from genetic defects of this developmental program, which requires a balance of neuronal proliferation, migration and apoptosis during brain development. It has recently been shown that the condition is genetically heterogeneous, with five genetic loci responsible for microcephaly having been identified[9].

Other causal mechanisms for postnatal onset microcephaly include primary or secondary cerebral atrophy of varied origin commonly associated with hypoxic-ischemic encephalopathy[10], aneuploidy[11], genetic syndromes such as cri-du-chat syndrome[12] or environmental agents, one example of which is fetal alcohol syndrome[13]. As to the frequency of microcephaly, the data are scant. Of 157 Australian aboriginal children less than 2 years of age that were admitted to hospital for malnutrition, while 37 (24%) were microcephalic on admission, only 21 (13%) had been microcephalic at birth. Thus, 11% developed microcephaly during the neonatal period[14].

There is a dilemma in the prenatal diagnosis of microcephaly by serial sonographic measurements of fetal head circumference, since the head circumference measurements do not fall appreciably below normal centiles until the third trimester of pregnancy[15]. Moreover, as shown in our case, a significant proportion will not be detectable at all by intrauterine cranial growth monitoring. Elucidation of the genes responsible for microcephaly is therefore important for both genetic counseling and prenatal diagnosis[16].

More sophisticated imaging techniques, such as sonographic assessment of the frontal lobe[2], power Doppler[5] and nuclear magnetic resonance imaging[17] have been suggested when no other brain abnormalities are present and these may provide a more sensitive indicator than the mere measurement of skull growth. In this case both the biparietal diameter and the head circumference were within normal ranges at birth. Transvaginal sonographic examination of the brain anatomy at 36 weeks, including frontal lobe measurements[5] and color and power Doppler assessment of the cerebral arterial circulation, revealed no obvious signs of abnormality and this was falsely reassuring.

Similar to postnatal growth charts, which differentiate between male and female growth patterns, we have re-established prenatal normal values by calculating sex-specific intrauterine head measurements from 4234 normal pregnancies with postnatal follow-up data available[6]. The use of these sex-specific growth charts at 38 weeks would have demonstrated the biparietal diameter and the head circumference to be on the 20th and 15th centiles, respectively, rather than just below the 40th centile. Using these sex-specific charts may raise suspicion in doubtful cases of microcephaly; however, even they may not allow the recognition of a substantial number of affected fetuses.

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