Prenatal Diagnosis of Monosomy 17p (17p13.3 → pter) Associated With Polyhydramnios, Intrauterine Growth Restriction, Ventriculomegaly, and Miller-Dieker Lissencephaly Syndrome in a Fetus

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SUMMARY

Objective: To present the prenatal magnetic resonance imaging (MRI) and ultrasound findings of Miller-Dieker lissencephaly syndrome (MDLS) associated with chromosome 17p13.3 deletion in a fetus.

Case Report: A 30-year-old, primigravid woman was referred to the hospital at 31 weeks' gestation because of intrauterine growth restriction (IUGR) and polyhydramnios detected by ultrasound. The pregnancy was uneventful until 31 weeks of gestation when IUGR and polyhydramnios were first noted. Level II ultrasound at 31 weeks' gestation showed fetal biometry equivalent to 27 weeks' gestation, an amniotic fluid index of 33.4 cm, ventriculomegaly, and abnormal sulcal development with absence of gyri and sulci, and a shallow Sylvian fissure. Other organs were unremarkable. Subsequent amniocentesis revealed a 46,*XY*,del(17)(p13.3) karyotype. Ultrafast fetal MRI performed at 34 weeks of gestation revealed agyria/pachygyria, a figure-eight appearance of the brain, a wide and shallow Sylvian fissure, enlarged subarachnoid space, ventriculomegaly, and polyhydramnios. At 35 weeks' gestation, a 1,346-g male baby was delivered with facial dysmorphism, characteristic of MDLS. Postnatal MRI confirmed the prenatal diagnosis.

Conclusion: Polyhydramnios, IUGR and ventriculomegaly are important prenatal ultrasound markers of MDLS. Prenatal diagnosis of these markers should include a detailed investigation of cerebral sulci and fissures, and genetic analysis for MDLS. Fetal MRI is helpful for the diagnosis of lissencephaly. [*Taiwan J Obstet Gynecol* 2009; 48(4):408–411]

Key Words: chromosome 17p13.3 deletion, lissencephaly, magnetic resonance imaging, Miller-Dieker syndrome, ultrasound, ventriculomegaly

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ELSEVIER

Introduction

Miller-Dieker lissencephaly syndrome (MDLS; OMIM 247200) is characterized by microcephaly, lissencephaly (a smooth brain without convolutions or gyri), and a distinctive facial appearance comprising prominent forehead, bitemporal hollowing, a short nose with upturned nares, a protuberant upper lip, and a small jaw. MDLS is an autosomal dominant disorder and can be caused by deletions or mutations of the *LIS1* gene (*PAFAH1B1*; OMIM 601545) on 17p13.3 [1]. Deletions of additional genes, such as *14-3-3ε* and *CRK*, in combination with deletions of *LIS1*, may contribute to the more severe form of lissencephaly seen only in patients with MDLS [2]. The incomplete development of the brain causes severe mental deficiency with initial hypotonia, opisthotonus, spasticity, and seizures in patients with MDLS [3]. Other central nervous system abnormalities associated with MDLS include an absent or hypoplastic corpus callosum, a large cavum septi pellucidi, and small midline calcifications in the region of the third ventricle [3]. MDLS may be associated with polyhydramnios, omphalocele [4], and neural tube defects [5]. Other occasional abnormalities include tetralogy of Fallot, ventricular septal defect, valvular pulmonary stenosis, intrauterine growth restriction (IUGR), decreased fetal activity, cystic dysplasia of the kidney, cleft palate, and cataract [3]. Here, we report the prenatal diagnosis of a chromosome 17p13.3 deletion associated with MDLS in a fetus, and present the prenatal magnetic resonance imaging (MRI) and ultrasound findings of this case.

Case Report

A 30-year-old, primigravid woman was referred to the hospital at 31 weeks' gestation because of IUGR and polyhydramnios detected by ultrasound. The woman and her husband were nonconsanguineous and healthy, and there was no family history of congenital anomalies. She did not have diabetes mellitus and denied any exposure to teratogenic agents or infectious diseases during this pregnancy. The pregnancy was uneventful until 31 weeks' gestation when polyhydramnios and IUGR were first noted on prenatal ultrasound. Level II ultrasound examination at 31 weeks' gestation revealed a singleton fetus with a biparietal diameter, an abdominal circumference and femur length equivalent to 27 weeks' gestation, an amniotic fluid index of 33.4 cm, ventriculomegaly, and abnormal sulcal development with absence of gyri and sulci, and a shallow Sylvian fissure (Figure 1). Other organs were unremarkable.

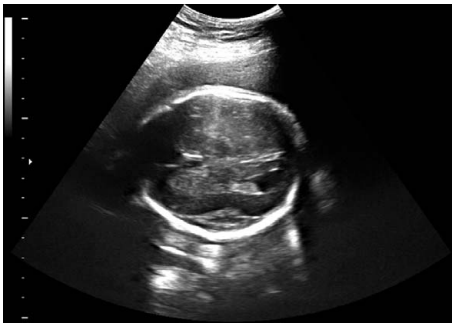

Figure 1. Prenatal ultrasound at 31 weeks' gestation showing ventriculomegaly and abnormal sulcal development with absence of gyri and sulci, and a shallow Sylvian fissure.

Lissencephaly was tentatively diagnosed. Subsequent amniocentesis revealed a 46, *XY*,del(17)(p13.3) karyotype. The parental karyotypes were normal. Chromosome 17p13.3 deletion was confirmed by comparative genomic hybridization. Ultrafast fetal magnetic resonance imaging (MRI) performed at 34 weeks' gestation revealed agyria/pachygyria, a figure-eight appearance of the brain, wide and shallow Sylvian fissures, enlarged subarachnoid space, ventriculomegaly, and polyhydramnios (Figure 2). Premature rupture of the membranes occurred at 35 weeks' gestation, and a 1,346-g male baby was delivered. He had a small head, wrinkling of the forehead, a broad nasal bridge, anteverted nares, epicanthal folds, micrognathia, a long, thin upper lip, and low-set ears. The body length was 40 cm ($< 5^{th}$ centile), the head circumference was 28 cm ($< 5^{th}$ centile), and the chest circumference was 23.5 cm ($< 5^{th}$ centile). Postnatal MRI of the brain showed lissencephaly with agyria/pachygyria and ventricular dilation. A final diagnosis of MDLS was made. At the age of 10 months, the infant suffered from growth retardation, developmental delay, and seizures.

Discussion

The present case manifested ventriculomegaly, IUGR and polyhydramnios on prenatal ultrasound performed in the third trimester. Common sonographic findings in fetuses with MDLS include widespread agyria, abnormal Sylvian fissures and insula, ventriculomegaly (usually mild), corpus callosum dysgenesis, microcephaly, IUGR, and polyhydramnios, while less common findings include micrognathia, congenital heart defects, genitourinary anomalies, and omphalocele [6,7].

Prenatal diagnosis of lissencephaly and MDLS is unusual, because evaluation of the cerebral cortex is not routinely included in fetal ultrasound anatomic investigations. Greenberg et al [8] reported a fetus with a deletion of 17p13, IUGR, double-outlet right ventricle,

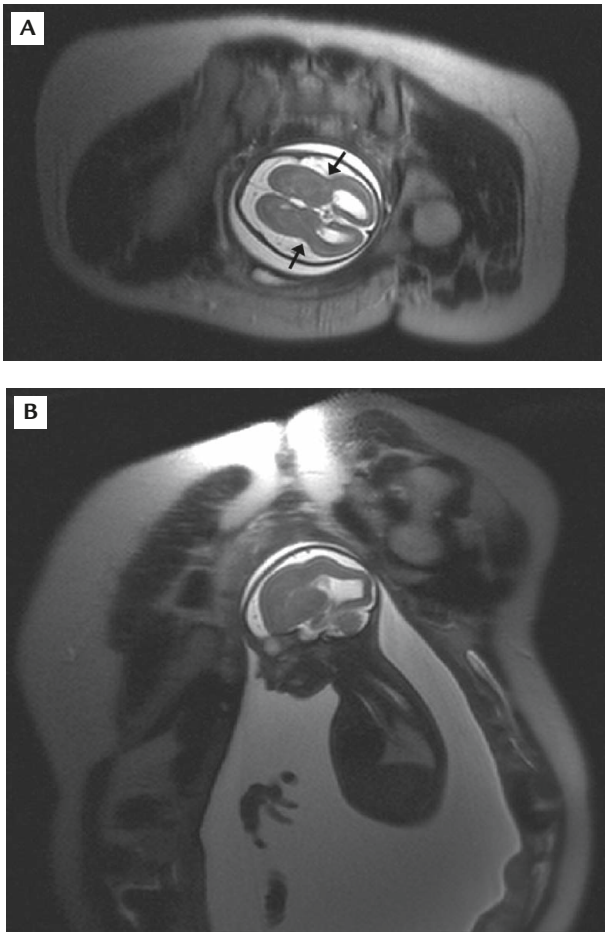

Figure 2. (A, B) Fetal magnetic resonance imaging at 31 weeks' gestation showing agyria/pachygyria, a figure-eight appearance of the brain, wide and shallow Sylvian fissures (arrows), enlarged subarachnoid space, ventriculomegaly, and polyhydramnios.

thymic hypoplasia, and polyhydramnios. Saltzman et al [9] first reported prenatal diagnosis of MDLS by ultrasound in two fetuses. The first case was referred for high-risk obstetric management and serial ultrasound examinations because of a family history of lissencephaly and maternal balanced translocation involving chromosome 17p13. The fetus had MDLS with monosomy 17p (17p13 → pter), and presented with polyhydramnios at 25 weeks' gestation and a smooth gyral pattern on ultrasound at 31 weeks' gestation. The second case was referred for prenatal sonographic survey because of IUGR. The fetus had MDLS with a deletion of one chromosome 17 at 17p13.3, and presented with severe polyhydramnios, tetralogy of Fallot, and smooth gyri on ultrasound at 31 weeks' gestation. Blaas et al [10] reported prenatal diagnosis of MDLS and a 17p deletion at 17p13.2 in a fetus with prenatal sonographic findings of polyhydramnios, agenesis of the corpus callosum, and an abnormal brain showing a total lack of sulci and gyri at 27 weeks' gestation. Okamura et al [11] reported prenatal diagnosis of lissencephaly in two cases with normal karyotypes. Fetal MRI showed a smooth brain surface and remarkable Sylvian fissures that were barely detectable by ultrasound. The first case had bilateral ventriculomegaly, smooth surface of the cortex, large Sylvian fissures, and dilation of the lateral ventricles on fetal MRI at 31 weeks' gestation. The second case had bilateral ventriculomegaly at 24 weeks' gestation, smooth surface of the brain, and remarkable Sylvian fissures on fetal MRI at 31 weeks' gestation. McGahan et al [12] reported a fetus with MDLS and del(17)(p13.3) associated with polyhydramnios and ventriculomegaly on prenatal ultrasound at 34 weeks' gestation. Chitayat et al [13] reported prenatal diagnosis of omphalocele and mild cerebral ventriculomegaly in a fetus with MDLS and a deletion in 17p13.3. Greco et al [14] reported prenatal diagnosis of isolated lissencephaly by MRI at 24 weeks' gestation because of asymmetrical ventricular dilation on ultrasound in a fetus. The result of a 17p monosomy test was negative. Fong et al [6] reported prenatal diagnosis of MDLS in three cases in which agyria and lissencephaly were prospectively suspected by ultrasound at 23, 26 and 30 weeks' gestation. The lissencephaly in these cases was subsequently confirmed by prenatal MRI. In a review of seven fetuses with MDLS with chromosome 17p13.3 deletions, Fong et al [6] found that all fetuses had delayed cortical development that could be identified by ultrasound after 23 weeks' gestation. In these fetuses with MDLS, abnormal prenatal findings, in addition to delayed cortical development, included ventriculomegaly ($n=6$), polyhydramnios ($n=3$), IUGR ($n=3$), micrognathia ($n=1$), and omphalocele ($n=1$). Pastorino et al [15] reported prenatal diagnosis of lissencephaly by fetal MRI at 35 weeks' gestation following the sonographic observation of isolated borderline ventriculomegaly in a fetus with a normal karyotype. Lenzini et al [16] reported a fetus with prenatal diagnosis of MDLS associated with an apparently balanced 46,XX,t(17;18)(p13;p11.2) but a 4-Mb microdeletion at 17p13.3. The fetus manifested polyhydramnios, IUGR, microcephaly, ventriculomegaly, dysgenic corpus callosum, hypoechogenic cerebral parenchyma, pachygyria, equinovarus foot, and hyperechoic renal parenchyma on prenatal ultrasound at 29 weeks' gestation. Aslan et al [17] reported prenatal diagnosis of lissencephaly by fetal MRI at 27 weeks of gestation in a fetus with ventriculomegaly and a 46,XY karyotype.

In conclusion, the present case demonstrates that polyhydramnios, IUGR, and ventriculomegaly are important prenatal ultrasound markers of MDLS. Prenatal diagnosis of these markers should include a detailed investigation of cerebral sulci and fissures, and genetic

analysis of MDLS. Fetal MRI is helpful for the diagnosis of lissencephaly.

Acknowledgments

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