



Prenatal Diagnosis of Lissencephaly Type 2 using Three-dimensional Ultrasound and Fetal MRI: Case Report and Review of the Literature

Diagnóstico pré-natal de lissencefalia tipo 2 por meio da ultrassonografia e ressonância magnética fetal: relato de caso e revisão da literatura

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Abstract

Keywords

- ▶ lissencephaly
- ▶ cobblestone cortex
- ▶ genetic counseling
- ▶ magnetic resonance imaging
- ▶ pathology
- ▶ prenatal diagnosis
- ▶ three-dimensional ultrasound

Lissencephaly is a genetic heterogeneous autosomal recessive disorder characterized by the classical triad: brain malformations, eye anomalies, and congenital muscular dystrophy. Prenatal diagnosis is feasible by demonstrating abnormal development of sulci and gyri. Magnetic resonance imaging (MRI) may enhance detection of developmental cortical disorders as well as ocular anomalies. We describe a case of early diagnosis of lissencephaly type 2 detected at the time of routine second trimester scan by three-dimensional ultrasound and fetal MRI. Gross pathology confirmed the accuracy of the prenatal diagnosis while histology showed the typical feature of cobblestone cortex. As the disease is associated with poor perinatal prognosis, early and accurate prenatal diagnosis is important for genetic counseling and antenatal care.

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Resumo**Palavras-chave**

- ▶ lissencefalia
- ▶ *cobblestone* córtex
- ▶ aconselhamento genético
- ▶ ressonância magnética
- ▶ patologia
- ▶ diagnóstico pré-natal
- ▶ ultrassom tridimensional

Lissencefalia são doenças genéticas autossômicas recessivas heterogêneas caracterizadas pela tríade clássica: malformações do cérebro, anomalias oculares e distrofia muscular congênita. Diagnóstico pré-natal é factível pela demonstração do desenvolvimento anormal de sulcos e giros. Ressonância magnética (RM) melhora a detecção de distúrbios do desenvolvimento cortical, bem como as anomalias oculares. Descrevemos um caso de diagnóstico precoce de lissencefalia tipo 2 detectado no momento do ultrassom morfológico de segundo trimestre pela ultrassonografia tridimensional e RM fetal. A macroscopia confirmou a acurácia do diagnóstico pré-natal, enquanto que a microscopia mostrou a típica característica de córtex em *cobblestone*. Como a doença está associada a um pobre prognóstico perinatal, o precoce e acurado diagnóstico pré-natal é importante para o aconselhamento genético e seguimento da gestação.

Introduction

Lissencephaly is a genetic heterogeneous autosomal recessive disorder characterized by the classical triad: brain malformations, eye anomalies, and congenital muscular dystrophy.¹ This disease was first described by Walker² in 1942 as lissencephaly; however, the spectrum of brain abnormalities is diverse, including Dandy-Walker syndrome and ventriculomegaly.^{3,4} The neuropathology of lissencephaly relies upon cortical dysplasia that results in neuroglial over-migration into the arachnoid space to form an extracortical layer that produces agyria and/or a “cobblestone” brain surface and ventricular enlargement.⁵ Radial glial cells play a central role in cerebral cortical development⁶ in addition, the basement membrane/glia limitans (BM/GL) located immediately below the pia mater serves as an anchor point for the end feet of radial glial cells and as a physical barrier to migrating neurons.⁷ Mutations in genes encoding BM constituents have been shown to disrupt BM integrity and result in disorganized cortical lamination.⁸⁻¹⁰ Mutations in *POMT1*, *POMT2*, *POMGNT1*, *LARGE*, *FKTN*, and *FKRP* identified these diseases as α -dystroglycanopathies.⁵ Mutations in the *POMT1* (protein-O-mannosyltransferase 1) gene in the 9q34 chromosome region account for ~20% of lissencephaly diseases;¹¹ however, mutations in the *LARGE* (Acetylglucosaminyltransferase-like Protein) and *FKRP* (Fukutin-Related Protein) have also been described in the literature.^{12,13} In zebrafish, mutation in *LAMB1* (laminin subunit 1), a glycoprotein of the basal lamina that influences cell proliferation, differentiation, migration, and adhesion,¹⁴ has been shown to cause cobblestone lissencephaly without muscular and ocular malformations.¹⁵ The main cortical fissures can be visualized through ultrasound from 18 weeks of gestation onwards; however, only at 30-32 weeks the main sulci/gyri can be visualized.¹⁶ Three-dimensional ultrasound was introduced in the obstetrics clinical practice in the mid-90's, and has been applied as adjuvant to 2DUS and magnetic resonance imaging (MRI) in several fetal brain malformations. However, the application of three-dimensional ultrasound (3DUS) in the rendering

mode to assess the development of fetal sulci and gyri during pregnancy is still of limited application.¹⁷

Case Report

A 28-year-old-woman, gravida 1, was referred for level II ultrasound examination at 21 weeks and 5 days of gestation for suspected severe hydrocephalus in the Department of Obstetrics and Gynecology, Ospedale Civile di Guastalla, AUSL Reggio Emilia, Reggio Emilia, Italy. Her past medical and family history was investigated and resulted uneventful, with no congenital anomalies. Consanguinity was also excluded. TORCH investigation showed no evidence of primary infection during pregnancy. Body mass index (BMI) was 24 kg/m², normal blood pressure and 75 g oral glucose tolerance test (OGTT) performed at the 16th week of gestation for ethnicity resulted negative. Ultrasound examination was performed using Voluson E6 apparatus (GE, Milwaukee, WI) equipped with both transabdominal and transvaginal 2D/3D volumetric probes. Fetal biometry showed a growth within the range for the gestational age. Neuroscan using conventional 2DUS confirmed the diagnosis of a severe communicating hydrocephalus. As part of our protocol in case of detected brain malformations, dedicated 3DUS neuroimaging using surface rendering mode was performed and enabled, better than 2DUS, detection of a thin mantle of cortex with absent visualization of the parieto-occipital and calcarine fissures, findings consistent with pachygyria (▶ **Fig. 1**). There was associated posterior fossa abnormality characterized by cerebellar vermis hypoplasia with a transverse cerebellar diameter of 14 mm (< 3rd percentile for expected gestational age). A prenatal ultrasound diagnosis of lissencephaly was prompted. A thorough anatomical survey excluded other malformations, including ocular, facial, cardiac or skeletal diseases. Following genetic counselling and the signed informed consent, an uneventful amniocentesis with fluorescence in situ hybridization (FISH) investigation was performed. Fetal karyotype resulted in 46,XY and FISH excluded a 17p13.3 deletion or mutation in the *LIS1* gene encoding for Miller-Dieker syndrome (lissencephaly type I). Fetal MRI was at that time arranged as complementary

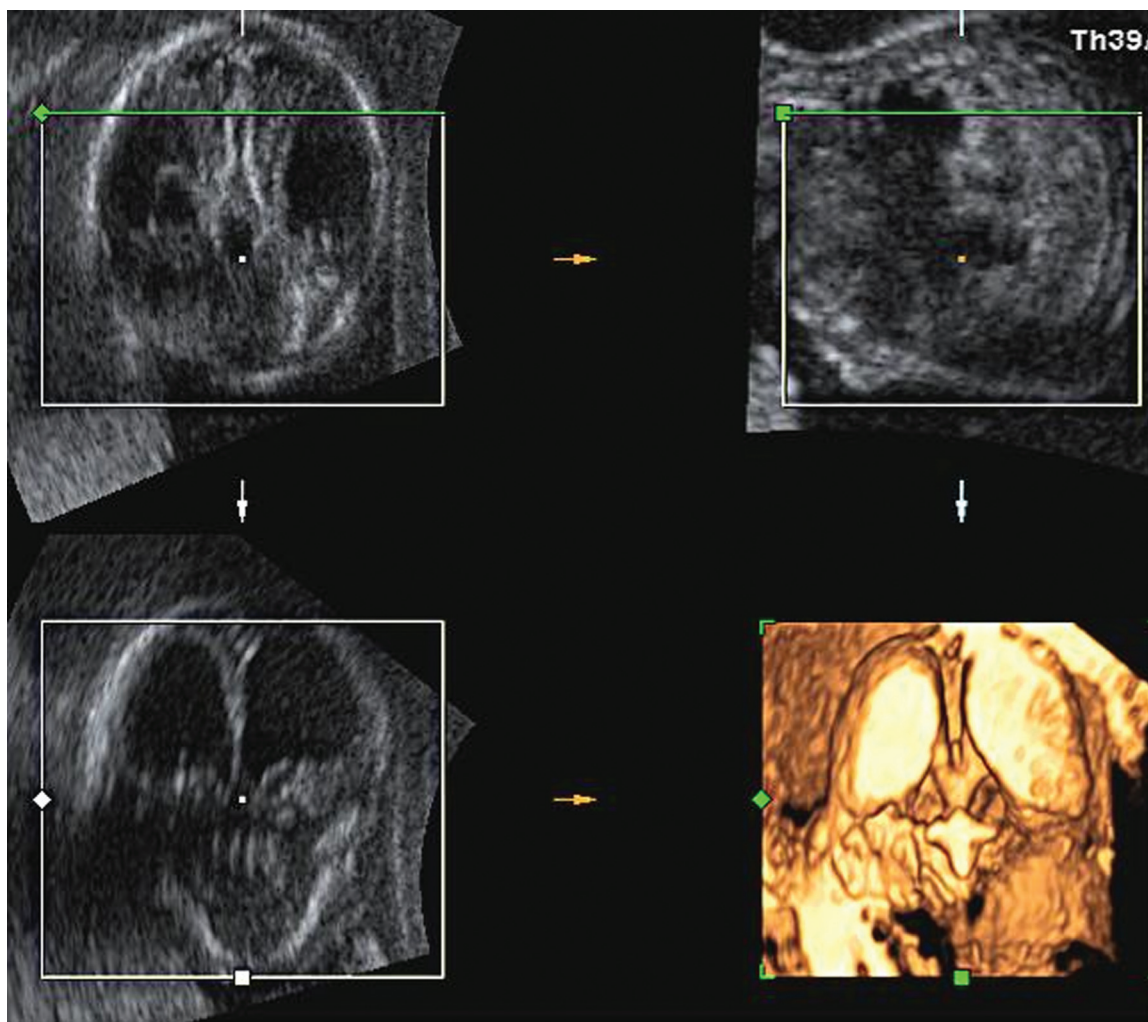


Fig. 1 Transabdominal three-dimensional ultrasound in rendering mode performed at 21 weeks and 5 days of gestation. Navigation within the volume detected severe communicating hydrocephalus. Abnormal posterior fossa with cerebellar hypoplasia was also detected, as well as a thin mantle of cortex. No parieto-occipital fissure or calcarine sulcus could be observed.

diagnostic investigation. The MRI equipment was a 1.5 Tesla Signa Twin Speed superconducting system (GE, Milwaukee, WI) using an 8-element phased array surface coil. Standard single-shot fast spin echo (SSFSE) imaging was performed in the fetal sagittal, coronal, and axial planes using the following parameters: repetition time (RT), single-shot, echo time (ET), 80 milliseconds; TR/TE, Infinite/90; bandwidth, 32 kHz; field of view, 30×30 cm; matrix, 256×192 ; gap, 1.5 mm; number of excitations, 0.5; refocusing pulse of less than 180 degrees; slice thickness, 4 mm; and 0.6 second per slice, echo-train length, 72; 1 signal acquired. Fetal MRI confirmed the ultrasound findings of communicating hydrocephalus with posterior fossa anomalies including cerebellar vermal hypoplasia, brainstem hypoplasia and pachygyria (**Fig. 2**). Post-test counselling by the multi-specialist team was provided due to poor perinatal prognosis of the disease, parents requested pregnancy termination that was achieved after hospitalization and accomplished using vaginal PGE administration. Gross pathology documented a visible Sylvian fissure but with a vertical direction, wide communication of the dilated frontal horns with dysplasia of the anterior wall of the cavum septi pellucidi (absent, a finding also seen

in septo-optic dysplasia and semilobar holoprosencephaly), normal corpus callosum and dilated fourth ventricle. Cerebellar hypoplasia was confirmed.

Histology showed the typical cobblestone pattern of the cerebral cortex in lissencephaly type 2. Cortical layers were absent and there was an irregular scramble of neurons mixed with underlying white matter. These findings represented the neuropathology clues of the so-called cobblestone cortex at cellular level. Normal fetal cortex at 22 weeks was still unlayered, but was well organized, and future neurons were orderly piled up (**Fig. 3**).

Macroscopy of fetal brain showed that the cortical surface was smooth (agyria). The normal gray-white matter distribution was not recognizable, but there was evidence of a discontinuous subcortical gray line. Lateral ventricles were enlarged and hippocampi were upright (**Fig. 4**).

Discussion

Lissencephaly is a generic term used to describe different congenital brain malformations resulting from disorders in the migration of neocortical neurons during the 3rd and 4th



Fig. 2 (A) T2-weighted fetal magnetic resonance imaging confirmed in coronal section the findings of communicating hydrocephalus (double arrow), cerebellar hypoplasia (c) and pachygyria (*); (B) T2-weighted image in sagittal plane showed brainstem hypoplasia with typical “Z”-shaped morphology (black arrow) and dilated fourth ventricle. The mantle of the cerebral cortex was characterized by pachygyria (asterisk). A diagnosis of lissencephaly was elicited.

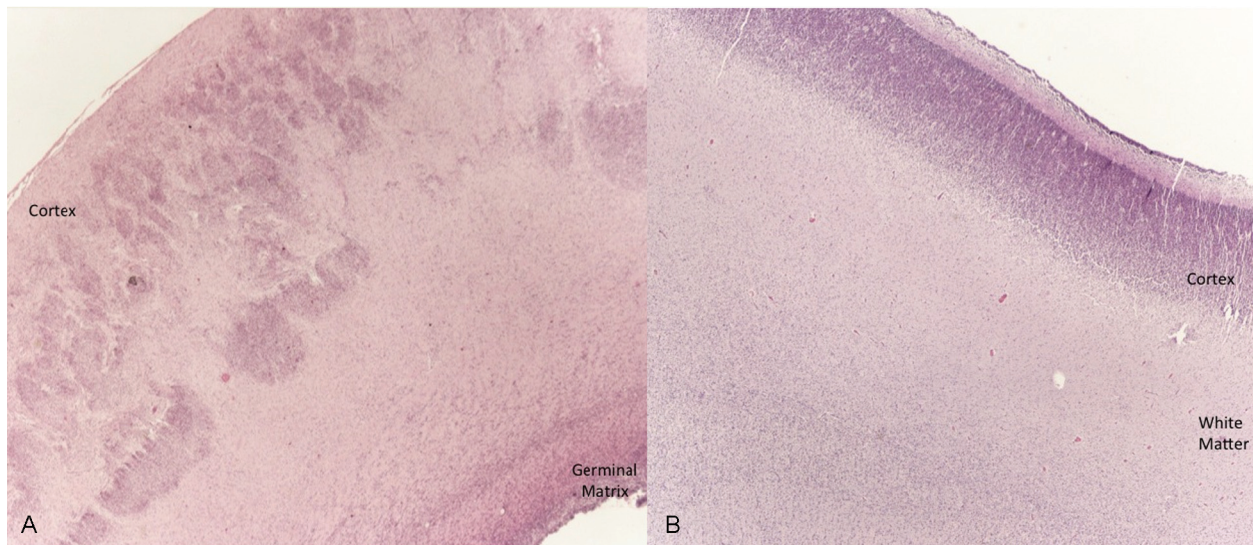


Fig. 3 (A) Histology shows the typical cobblestone pattern of the cerebral cortex in lissencephaly type 2. Cortical layers are absent and there is an irregular scramble of neurons mixed with underlying white matter. (B) Histology shows normal fetal cortex at 22 weeks of gestation. The primitive neurons, migrating from the germinal matrix, are orderly piled up. No definite layers are recognizable yet.

months of gestation.¹⁸ Lissencephaly has been divided in three sub-types. Lissencephaly type 1 can be isolated or associated with several phenotypes overlapping those of Miller-Dieker or Norman-Roberts syndrome. Miller-Dieker syndrome is a genetic disorder associated with a mutation or deletion at chromosome 17p13.3,¹⁹ a finding that was excluded in our observation by FISH. In 50% of cases, lissencephaly type 2 is characterized by a disorganized, unlayered cortex, ventriculomegaly and Dandy-Walker syndrome. Aqueduct stenosis or posterior encephalocele are also sometimes found.²⁰ Over the last decade, lissencephaly type 3 has been used to describe a phenotype lacking radiologic and pathologic findings, as seen in type 1 or lissencephaly type 2. This latter form is a lethal familial syndrome that comprises

microcephaly/lissencephaly and a spectrum of abnormalities lined to a severe fetal akinesia deformation sequence.²¹

Prenatal diagnosis of lissencephaly and overlapping syndromes has been described since the mid-1980s by conventional 2DUS.²² Lissencephaly is usually detected late in gestation using 2DUS² and ventriculomegaly is described in almost all cases diagnosed prenatally.²³⁻²⁵ Although the neuronal migration process reaches its peak at around 20 weeks of gestation, the sensitivity of ultrasound in the prenatal diagnosis of abnormal cortical development is low. However, Malinger et al²⁶ demonstrated that dedicated neurosonography using transabdominal route showed good level of agreement between prenatal diagnosis of abnormal cortical development and pathology examination,



Fig. 4 Macroscopy of fetal brain shows a coronal section through the midline. The cortical surface is smooth (agyria). The normal gray-white matter distribution is not recognizable, but there is evidence of a discontinuous subcortical gray line (arrow). Lateral ventricles are enlarged and hippocampi are upright.

both macro- and microscopic. Toi et al²⁷ assessed the gestational age by which sulci were visible using trans-abdominal ultrasound in 50 normal fetuses between 15 weeks and 6 days and 29 weeks and 6 days of gestation. These authors demonstrated that sulci were always visible beyond week 20, and specifically the parieto-occipital fissure > 20w5d, calcarine sulcus > 21w9d, cingulate sulcus > 24w3d and convexity sulci > 27w9d.²⁷

Strigini et al²⁸ reported a case at week 26 of gestation in which 2DUS showed enlargement of the lateral and third ventricles, separated cerebellar lobes with no detectable vermian structure and an enlarged retropulvinar cistern.

Fetal MRI enhanced the prenatal ultrasound diagnostic accuracy of lissencephaly by showing a kinked “Z”-shaped brainstem, with bifid pons and medulla oblongata. These anatomical details were undiagnosed on 2D/3DUS, confirming the role of antenatal MRI as a complementary diagnostic tool in all cases of brain pathology detected by ultrasound. Although neuroscan for assessment of CNS malformations is routinely performed by 2DUS, 3DUS, with its applications such as multiplanar mode, reformatting/reslicing techniques, tomographic ultrasound imaging (TUI) and volume calculation may potentially aid the prenatal detection of brain anomalies and may be complemented by fetal MRI.^{29–32} As cortical and sulcus formation reflect the maturation of the brain, MRI provides most accurate information of sulci and gyri development compared with ultrasound, as

visibility is not affected by cranial bones with near reverberation artifacts or fetal position. Ghai et al³³ detected specific patterns of the development of sulci by 2DUS or MRI in fetuses with lissencephaly. Normally, the cerebral cortex develops in three overlapping stages: cell proliferation, neuronal migration, and cortical organization. Opposite to that, in cobblestone lissencephaly the cerebral cortex shows combined agyria and pachygyria, as well as polymicrogyria with a pebbled surface.

MRI findings consistent with cobblestone lissencephaly may be white matter signal abnormality, an irregular layer of ectopic neurons, corpus callosum hypoplasia, cerebellar hemisphere and vermis hypoplasia, brainstem hypoplasia with “Z”-shaped brainstem or notched pons.³⁴ In the cases in which fetal MRI cannot be arranged, 3DUS in the rendering mode has shown to improve the visualization of sulci and gyri, and this approach may be useful as a complementary diagnostic tool in the prenatal detection of cortical development disorders.¹⁵

Although very recently, Lacalm et al.³⁵ have reported ultrasound pattern of outer echogenic band reducing pericerebral spaces (corresponding to an infra and supratentorial extracortical layer of neuroglial over-migration on histology) and a “Z” shape-appearance of the brainstem at 14 weeks of pregnancy; caution must be exerted as the developing brain is still smooth and only severe forms, such as agyria, are likely to be diagnosed by 2DUS or early second trimester MRI.

Differential diagnoses include Dandy-Walker complex (DWC) and septo-optic dysplasia (SOD). Dandy-Walker complex refers to a spectrum of abnormalities of the posterior fossa categorized as classic DWM (enlarged posterior fossa, complete or partial agenesis of the cerebellar vermis, elevated tentorium); Dandy-Walker variant (variable hypoplasia of cerebellar vermis, with or without enlargement of the posterior fossa); and megacisterna magna (enlarged cisterna magna, with unaffected cerebellar vermis and fourth ventricle).^{36,37} Septo-optic dysplasia or De Morsier syndrome (OMIM #182230) can be caused by mutation in the homebox gene *HESX1* on chromosome 3p14 and it is clinically characterized by any combination of optic nerve hypoplasia, pituitary gland hypoplasia, and midline abnormalities of the brain, including absence of the corpus callosum and the septum pellucidum.³⁸ Cortical abnormalities in SOD may vary, ranging from schizencephaly, polymicrogyria and focal laminar disorganization of the cortical layers.

In summary, we have described an early second trimester diagnosis of lissencephaly using 3DUS and fetal MRI. Magnetic resonance imaging enhanced the accuracy of the ultrasound by detecting the abnormalities involving the brainstem, improved counselling accuracy and aided the parent’s decision-making process. Molecular genetic testing excluded Miller-Dieker lissencephaly, while neuropathology demonstrated a cellular neuronal pattern characteristic of a cobblestone cortex. We believe that dedicated 3DUS neuroscan and MRI are useful imaging modalities that contribute to the accurate detection of cortical disorders in the fetus even at early stages of development.

Note

Study performed at the Dipartimento di Ostetricia e Ginecologia, Ospedale Civile di Guastalla, AUSL Reggio Emilia, Reggio Emilia, Italy.

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