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REVIEW ARTICLE

Malformations of Cortical Development

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ABSTRACT

Cerebral cortical malformations are common causes of neurodevelopmental delay and epilepsy and include a wide range of antenatal neurogenesis disorders. Abnormal cell proliferation leads to microcephaly or megalencephaly, incomplete neuronal migration results in heterotopia and lissencephaly, neuronal overmigration manifests as cobblestone malformations, and anomalous postmigrational cortical organization is responsible for polymicrogyria (PMG) and schizencephaly. Although corticogenesis occurs early, these rare pathologies are associated with late onset during pregnancy, which does not allow their early prenatal recognition. This review aims to give an update of current knowledge of these insidious cerebral cortical disorders.

Keywords: Cerebral cortical malformations, Fetus, Ultrasound.

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INTRODUCTION

Cerebral cortex malformations may be the result of events that inhibit or alter neuronal and glial proliferation and differentiation, neuronal migration, and cortical maturation. Neuronal proliferation begins at the 7th week in the subependymal region at the walls of the lateral ventricles, resulting in being really highly active between the 13th and 24th weeks of gestation.[1] Neurons start to migrate at 8th week from the ventricular zone (germinal matrix) toward the pial surface of the developing cortex, along radially oriented glial scaffolds forming a transient laminar pattern.[2] Radial neuronal migration ends with the disappearance of the germinal matrix at 28 gestational weeks, getting the six layers of which the cerebral cortex is formed.[3] Gyration and sulcation occur when migration is completed after 32 weeks.[4] The pathognomonic pathological feature of neuronal disorders is due to an anomaly of neuronal migration related to defect of the glia limitans, which normally represents a mechanical barrier to migration and permits cortical lamination. The glia limitans is formed as early as 6 weeks and comprises a meshwork of astrocytic endfeet, attached by a junction complex to a distinct outer basal lamina, which is of pial origin. The α-dystroglycans have a key-rule for the attachment of the lamina and must undergo glycosylation to become functional. Hypoglycosylation of dystroglycans induces disruption of the glia limitans and consequent abnormal migration into the subarachnoid space.[5]

The pathogenic noxa responsible for neuronal disorders can be congenital due to genetic or metabolic anomalies, or can be secondary to infection [cytomegalovirus (CMV), Toxoplasma, Herpes virus], to a hypoxic/ischemic injury, to maternal diabetes, teratogen factors, and phenylketonuria. Local or global injury depends upon the time of exposition to the pathogenic noxa and the type of noxa.[6]

The most commonly used classification of anomalies of the cerebral cortex is that proposed by Barkovich et al,[1] which takes into account four types of anomalies based on the moment that the noxa occur during the phase of the formation of the cortex:

1. *Anomalies of neuronal proliferation*: Microcephaly, macrocephaly or megalencephaly, unilateral megalencephaly.
2. *Anomalies of neuronal migration*: Periventricular nodular heterotopia, types 1 and 2 lissencephaly.
3. *Anomalies of cortical organization*: Polymicrogyria, schizencephaly.
4. Unclassifiable anomalies related to congenital metabolic disorders.[1]

NEURONAL PROLIFERATION DISORDERS

Microcephaly is the result of a reduced glial and neuronal proliferation and increased apoptosis. The etiology is based on a primary genetic disorder or secondary to environmental noxae (infections, toxic agents, maternal phenylketonuria, alcohol, drugs). In recent years, the incidence seems to be on the rise due to the spread of Zika virus, which has a tropism for fetal neurons causing their apoptosis. The major effect of Zika virus seems to be when the exposition occurs in the first trimester, but injures cannot be excluded during the third trimester.

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The primary microcephaly can result from an autosomal, recessive, or X-linked inheritance pattern; the brain retains a normal gyration with less neurons than normal. The secondary microcephaly shows less and reduced depth gyri.[7]

Microcephaly is an evolutionary pathology, since the head growth deficiency is a process that takes time to manifest and, therefore, in many cases, prenatal diagnosis is not feasible. Leibovitz et al[8] have shown how about 90% of cases of microcephaly diagnosed at birth had a normal cranial circumference in the second trimester. Microcephaly is often associated with structural anomalies of the central nervous system (CNS), such as the cerebellum or corpus callosum anomaly.

The ultrasound prenatal diagnosis is based on the head circumference estimated below the 2nd standard deviation (SD) or inferior of the 3rd percentile for the gestational age; especially when gestational age is not certainly known, an additional diagnostic aid is the comparison of the head circumference to the abdominal circumference and to the femur length. The head circumference/abdominal circumference ratio >3 SD and a femur length/head circumference ratio <3 SD for the gestational age are suspicious findings of microcephaly. Since the failure of brain development mainly is of interest to the forebrain, an abnormal fetal profile with a flat and low frontal pole (Fig. 1) sometimes together with wide subarachnoid spaces are a further sonographic sign of microcephaly.[9] Differential diagnosis is with craniosynostosis in which the shape of the skull is unusual, with a small head in cases of fetal growth restriction and constitutional small head. Prognosis is poor and depends on the cause of microcephaly and other cerebral anomalies associated. The diagnostic workup includes evaluation of the fetal karyotype with array-comparative genomic hybridization (CGH), serum and amniotic tests for infections and fetal magnetic resonance imaging (MRI).

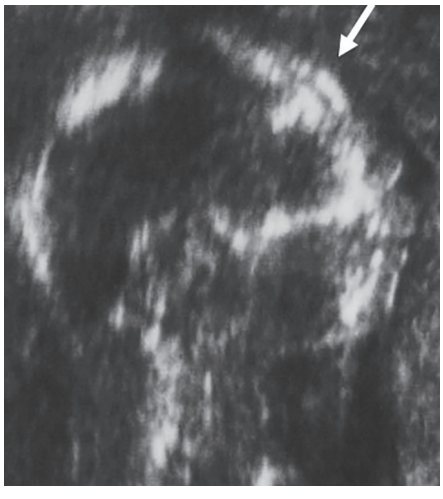


Fig. 1: Microcephaly. An abnormal fetal profile with a flat and low frontal pole (arrow) is visible

Macrocephaly or megalencephaly is defined as the presence of a head circumference above 2 SD (or > 98th percentile) for the gestational age with no evidence of hydrocephaly or intracranial masses. Autosomal dominance inheritance pattern is the most frequent form; concomitant identification of wide subarachnoid space in the frontal pole would be suggestive that macrocephaly can be related to familiar inheritance. It is essential to evaluate head circumference in the parents. This form is not related to a cognitive delay.

The differential diagnosis is with syndromic macrocephaly, unilateral megalencephaly, and overgrowth syndrome. The syndromic macrocephaly is rare and it is often associated with other anomalies of the CNS. Particularly MPPH syndrome(megalencephaly, polymicrogyria, postaxial polydactyly and hydrocephalus), MEG-PMG-MegaCC syndrome(megalencephaly, polymicrogyria, mega corpus callosum) or MCAP syndrome(macrocephaly capillary malformation) should be taken into account. Macrocephaly can be distinguished from the unilateral megalencephaly because in the latter, the cerebral hemispheres are asymmetric. At last, the differential diagnosis with overgrowth syndrome, such as Sotos syndrome, is made in case of other anomalies that involve CNS (dilation of the lateral cerebral ventricles, hypoplasia of the corpus callosum).

In all fetuses with macrocephaly, it is appropriate to verify the correct gestational age defined in the first trimester, the relationship with the other fetal biometric parameters and family history of previous macrocephaly. Karyotype and fetal MRI should be counseled with the parents according the gestational age.

Genetic syndromes can be associated and genetic counseling is mandatory.[8,10]

Unilateral megalencephaly is an extremely rare condition characterized by a unilateral abnormal growth of a cerebral hemisphere in comparison with the opposite one. It can be isolated or associated with genetic syndromes, such as tuberous sclerosis or Proteus syndrome. On ultrasound, an asymmetry between the two hemispheres with shifted midline structures and unilateral ventriculomegaly is shown (Fig. 2). It can be associated with other CNS anomalies (ventriculomegaly, agenesis of the corpus callosum, posterior fossa anomalies) with a thickening of the cerebral cortex and formation of abnormal gyri and sulci for the gestational age. The contralateral cerebral hemisphere is normal, but it is pressed. The differential diagnosis includes intracranial tumors, hemorrhage, and infections. Outcome is related to the damage of the cerebral hemispheres with psychomotor retardation, epilepsy, and hemiparesis of the opposite

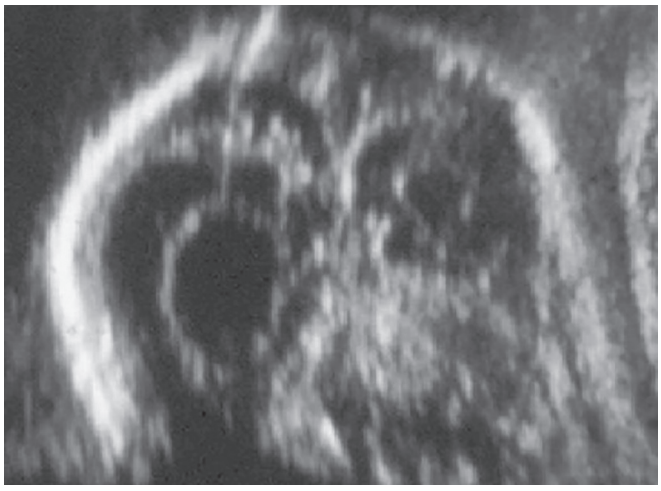


Fig. 2: Unilateral megalencephaly. The coronal section on the occipital lobes has an asymmetry between the two hemispheres with shifted midline structures and unilateral ventriculomegaly

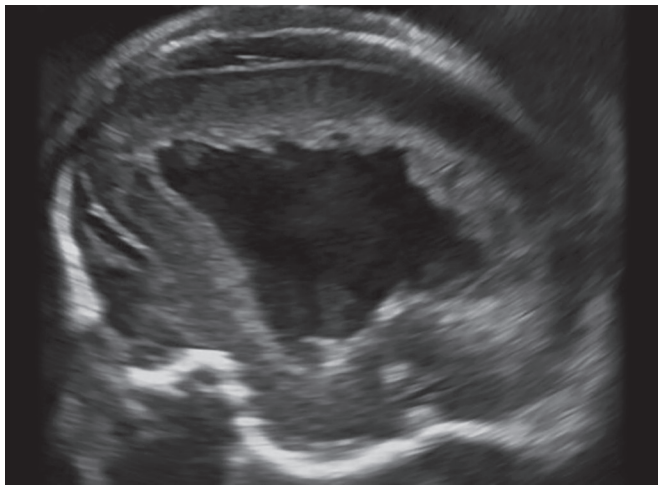


Fig. 3: Periventricular nodular heterotopia. Irregular surface of the enlarged lateral ventricle and periventricular hyperechogenicity may be recognized

side to that of the cerebral hemisphere involved. Fetal MRI, karyotype with array-CGH, and genetic counseling are recommended.[11-13]

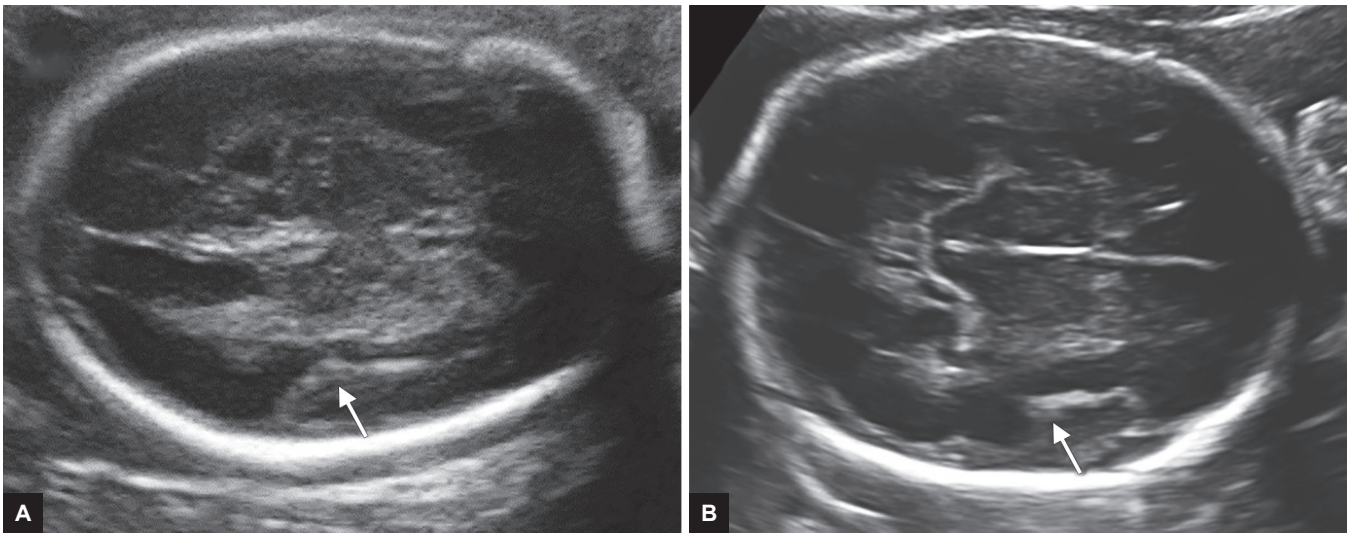
NEURONAL MIGRATION DISORDERS

Periventricular nodular heterotopia is a cerebral malformation due to neuronal agglomerate displacement for a neuronal migration block. Two types are identified: the periventricular type, with nodules surrounding the wall of the lateral ventricles; the stripe type, also called double cortex, with a neuronal lamina in the subcortical space. The first type is related to an X-linked dominant inheritance. Prenatal sonographic diagnosis is rare, with irregular surface of lateral ventricle, periventricular hyperechogenicity (Fig. 3), or small focal hyperechogenicity of cortex less than 2 mm. Associated anomalies can be possible, such as ventriculomegaly, posterior fossa anomaly, or corpus callosum agenesis. Differential diagnosis is with tuberous sclerosis and subependymal hemorrhage. The first one is distinguished because cardiac rhabdomyomas and intraparenchymal hyperechogenicity with diameter greater than 2 mm are visible. In case of subependymal hemorrhage, intraventricular hemorrhage is often associated. Normal neuronal development or mild grade mental retardation is shown in isolated cases, with variable degree epilepsy. The ultrasound suspect must be confirmed with fetal MRI. Karyotype, array-CGH, and genetic analysis for the FLN1 gene mutation must be suggested with genetic counseling to evaluate a possible risk of recurrence.

Lissencephaly refers to a smooth outer brain surface, characterized by the reduction (pachygiria) or absence (agyria) of the cerebral gyri and of the thickness of the cortex.[14] Based on brain pathology, lissencephaly is classified into two groups:

- *Type I lissencephaly, also called classic lissencephaly (agyria)*: cerebral cortex is composed of four layers, instead of the traditional six, as a result of incomplete migration of neurons. It appears as complete or incomplete agyria. The complete form is characterized by a smooth surface of the entire brain. In the incomplete form, which is the more commonly seen type, there is a gradient of severity either anterior to posterior or posterior to anterior depending on the genetic defect. Lissencephaly is usually symmetric. Agenesis of the corpus callosum or cerebellar hypoplasia can be associated findings depending on the affected gene. It is also associated with a phenotype similar to Miller–Dicker or Norman–Roberts syndrome.
- *Type II lissencephaly, also called Cobblestone complex*: irregular cerebral cortex with distorted cytoarchitecture (cobblestone shape), as a result of lack of connection of the radial glia to the pial limiting membrane and neuronal overmigration through pial gaps. It is accompanied by ocular anomalies and congenital muscular disorders. Cobblestone malformations have been divided into three different groups based on severity, with Walker–Warburg syndrome being the most severe form, Fukuyama congenital muscular dystrophy the mildest form, and muscle–eye brain disease being the moderate form. Congenital muscular dystrophy is a key feature.[13,14]

Type I lissencephaly is diagnosed by demonstration of dysgenesis of the Sylvian fissure (Fig. 4), delayed sulcal appearance, callosal abnormality, and cortical thickening or when the parieto-occipital, and calcarine fissure are not yet developed at 22 to 23 weeks. Mild ventriculomegaly and delayed opercular development are the earliest signs and can be depicted by 23 weeks of gestation in fetuses at risk.[15,16] Isolated



Figs 4A and B: (A) Lissencephaly at 26 weeks of gestation; and (B) the angle between the insula and the temporal operculum is still obtuse. Compare with the acute angle of a normal case

mild ventriculomegaly at the midtrimester scan should suggest a follow-up ultrasound examination at 24 to 25 weeks. The abnormal opercular formation is responsible for a "8" shaped brain.[17] Sometimes, the genetic defect can be suspected based on the gradient of the anomaly (anterior > posterior-DCX or posterior > anterior-LIS1), the fetal gender (male-DCX, ARX), associated brain anomalies (agenesis of corpus callosum-ARX, cerebellar hypoplasia-RELN, and abnormal basal ganglia-TUBA1A).[13] This diagnosis, however, is not easy and can be suspected only when associated intracranial anomalies are present or a familiar history is referred.[4,18]

Prenatal diagnosis of type II lissencephaly can be suspected when early enlargement of the lateral ventricles, abnormal vermis, retinal detachment, cataract, abnormal sulcation, kinked brain stem, and bifid pons are pointed out.[19-23] Kinked brain stem was reported prenatally by Stroustrup Smith et al[24] who used fetal MRI between 19 and 34 weeks in a unique series of seven cases, identifying an association between the Z-shaped appearance of the brain stem and the occurrence of severe neurodysgenesis. Lacalm et al[18] suggest that the observation of a Z-shaped appearance of the brain stem surrounded by an echogenic band is pathognomonic for cobblestone lissencephaly.

The prognosis is poor and characterized by severe mental retardation, hypotonia, convulsions, epilepsy, and death during the first 5 years of life. Karyotype and genetic counseling are suggested to estimate the possible risk of recurrence.

NEURONAL ORGANIZATION DISORDERS

Polymicrogyria is a malformation of the cerebral cortex in which an excessive of gyral and sulcal shallow developments are present. The PMG is caused by an interruption in normal cerebral cortical development in the late neuronal migration or early postmigrational development periods.[14] It is not a single entity, but a spectrum of cortical malformations with the common feature being excessive gyration.[25] All have, in common, a derangement of the normal six-layered lamination of the cortex, an associated derangement of sulcation, and fusion of the molecular layer across sulci.[26] It is due to a X-linked or genic mutation or chromosome 16 genic mutation, or due to infection by CMV or Parvovirus B19, or due to an ischemic/hemorrhagic state secondary to the death of a twin in a monochorionic pregnancy. Variable portions of the cerebral cortex can be affected: It may be focal, multifocal, or diffuse, unilateral, bilateral, symmetrical, and asymmetrical. The most common location (in 60–70% of cases) is around the Sylvian fissure, particularly, the posterior aspect of the fissure; however, any part of the cerebral cortex, including the frontal, occipital, and temporal lobes, can be affected. The PMG may be an isolated malformation or it may be associated with other brain malformations, such as microcephaly or ventriculomegaly.

The cortical changes of PMG take place late in pregnancy and appear as localized and/or generalized absence of normal sulcation with multiple abnormal infoldings of the affected cortex.

Before the 24th week, the identification of this cortical malformation is quite difficult with both ultrasound and MRI. The diagnosis is based on the presence of sulci that are not expected according to the gestational age, abnormal opercular development, an irregular surface of the brain, mild ventriculomegaly associated with numerous sulci in the perisylvian area, and a prominent subarachnoid space overlying the cortical malformation. When the cause is CMV infection, other signs of brain infection are

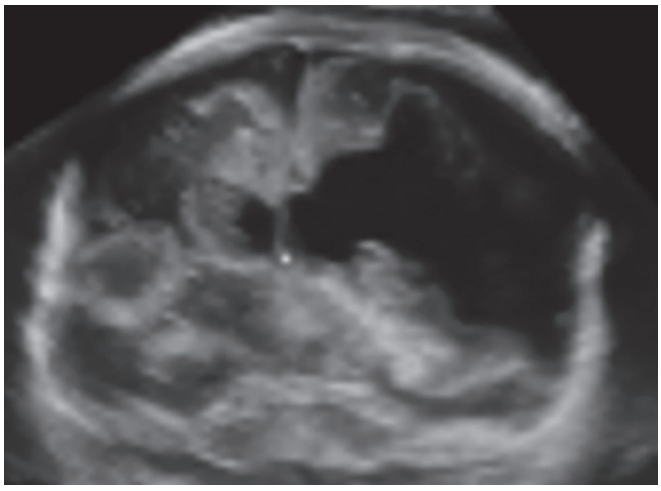


Fig. 5: Open lip schizencephaly. Coronal view: A large cleft in one hemisphere is visible

visible, such as ventriculomegaly, abnormal ventricular lining and adhesions, periventricular pseudocysts, temporal cysts, abnormal echogenicity of the white matter, calcifications, and cerebellar anomalies.

The prognosis depends on the extent and location of the affected area.[26-28]

Schizencephaly is a rare congenital anomaly in which a part of the brain cortex is absent, and the ventricular cavity widely communicates with the arachnoidal space. It can be unilateral or bilateral, symmetric or asymmetric. Two types of schizencephaly are known: the first one with a very thin cleft (closed lip schizencephaly) where the lips can be closed, and the second one with an open wide cleft filled with cerebrospinal fluid and often associated with VM (open lip schizencephaly) (Fig. 5). The latter form is often associated with septo-optic dysplasia. The clefts are covered with gray substance, thus excluding a loss of substance from acquired causes. Only the open lip schizencephaly has been diagnosed *in utero*. Commonly, it is situated around the Sylvian fissure and the diagnosis is usually made in the third trimester of pregnancy. The differential diagnosis with large porencephalic cysts located in the Sylvian fissure is extremely difficult. If it is visible as a small echogenicity and/or an irregular surface, it can be the porencephalic cyst, also called encephaloclastic cyst. Since the association between schizencephaly and septo-optic dysplasia is frequent, it is necessary to visualize the cleft in case of schizencephaly to rule out lobar holoprosencephaly and isolated septo-optic dysplasia. In cases of open lip schizencephaly, the prognosis is poor and it is generally associated with seizures and severe mental retardation.[29,30]

REFERENCES

1. Barkovich AJ, Kuzniecky RI, Jackson GD, Guerrini R, Dobyns WB. A developmental and genetic classification for malformations of cortical development. Neurology 2005 Dec;65(12):1873-1887.
2. Rakic P. Developmental and evolutionary adaptations of cortical radial glia. Cereb Cortex 2003 Jun;13:541–549.
3. Gupta A, Tsai LH, Wynshaw-Boris A. Life is a journey: a genetic look at neocortical development. Nat Rev Genet 2002 May;3(5):342-355.
4. Pugash D, Hendson G, Dunham CP, Dewar K, Money DM, Prayer D. Sonographic assessment of normal and abnormal patterns of fetal cerebral lamination. Ultrasound Obstet Gynecol 2012 Dec;40(6):642-651.
5. Devisme L, Bouchet C, Gonzal`es M, Alanio E, Bazin A, Bessi`eres B, Bigi N, Blanchet P, Bonneau D, Bonni`eres M, et al. Cobblestone lissencephaly: neuropathological subtypes and correlations with genes of dystroglycanopathies. Brain 2012 Feb;135(Pt 2):469-482.
6. de Wit MC, Lequin MH, de Coo IF, Brusse E, Halley DJ, van de Graaf R, Schot R, Verheijen FW, Mancini GM. Cortical brain malformations: effect of clinical, neuroradiological, and modern genetic classification. Arch Neurol 2008 Mar;65(3):358-366.
7. Stoler-Poria S, Lev D, Schweiger A, Lerman-Sagie T, Malinger G. Developmental outcome of isolated fetal microcephaly. Ultrasound Obstet Gynecol 2010 Aug;36(2): 154-158.
8. Leibovitz Z, Daniel-Spiegel E, Malinger G, Haratz K, Tamarkin M, Gindes L, Schreiber L, Ben-Sira L, Lev D, Shapiro I, et al. Prediction of microcephaly at birth using three reference ranges for fetal head circumference: can we improve prenatal diagnosis? Ultrasound Obstet Gynecol 2016 May;47(5):586-592.
9. Goldstein I, Reece EA, Pilu G, O'Connor TZ, Lockwood CJ, Hobbins JC. Sonographic assessment of the fetal frontal lobe: a potential tool for prenatal diagnosis of microcephaly. Am J Obstet Gynecol 1988 May;158(5):1057-1062.
10. Malinger G, Lev D, Ben-Sira L, Hoffmann C, Herrera M, Viñals F, Vinkler H, Ginath S, Biran-Gol Y, Kidron D, et al. Can syndromic macrocephaly be diagnosed in utero? Ultrasound Obstet Gynecol 2011 Jan;37(1):72-81.
11. Romero XC, Molina FS, Pastor E, Amaya F. Hemimegalencephaly: 2D, 3D ultrasound and MRI correlation. Fetal Diagn Ther 2011 Nov;29(3):257-260.
12. Toi A, Chitayat D, Blaser S. Abnormalities of the foetal cerebral cortex. Prenat Diagn 2009 Apr;29(4):355-371.
13. Lerman-Sagie T, Leibovitz Z Malformations of cortical development: from postnatal to fetal imaging. Can J Neurol Sci 2016 Sep;43(5):611-618.
14. Barkovich AJ, Guerrini R, Kuzniecky RI, Jackson GD, Dobyns WB. A developmental and genetic classification for malformations of cortical development: update 2012. Brain 2012 May;135(Pt 5):1348-1369.
15. Malinger G, Lev D, Lerman-Sagie T. Abnormal sulcation as an early sign for migration disorders. Ultrasound Obstet Gynecol 2004 Dec;24(7):704-705.
16. Toi A, Lister WS, Fong KW. How early are fetal cerebral sulci visible at prenatal ultrasound and what is the normal pattern of early fetal sulcal development? Ultrasound Obstet Gynecol 2004 Dec;24(7):706-715.
17. Fong KW, Ghai S, Toi A, Blaser S, Winsor EJ, Chitayat D. Prenatal ultrasound findings of lissencephaly associated with Miller-Dieker syndrome and comparison with pre- and

postnatal magnetic resonance imaging. Ultrasound Obstet Gynecol 2004 Dec;24(7):716-723.
18. Lacalm A, Nadaud B, Massoud M, Putoux A, Gaucherand P, Guibaud L. Prenatal diagnosis of cobblestone lissencephaly associated with Walker-Warburg syndrome based on a specific sonographic pattern. Ultrasound Obstet Gynecol 2016 Jan;47(1):117-122.
19. Farrell SA, Toi A, Leadman ML, Davidson RG, Caco C. Prenatal diagnosis of retinal detachment in Walker-Warburg syndrome. Am J Hum Genet 1987 Nov;28(3):619-624.
20. Monteagudo A, Alayón A, Mayberry P. Walker-Warburg syndrome: case report and review of the literature. J Ultrasound Med 2001 Apr;20(4):419-426.
21. Gasser B, Lindner V, Dreyfus M, Feidt X, Leissner P, Treisser A, Stoll C. Prenatal diagnosis of Walker-Warburg syndrome in three sibs. Am J Med Genet 1998 Mar;76(2):107-110.
22. Kojima K, Suzuki Y, Seki K, Yamamoto T, Sato T, Tanaka T, Suzumori K. Prenatal diagnosis of lissencephaly (type II) by ultrasound and fast magnetic resonance imaging. Fetal Diagn Ther 2002 Jan-Feb;17(1):34-36.
23. Strigini F, Valleriani A, Cecchi M, Ghirri P, Aiello C, Bertini E, Cioni G, Battini R. Prenatal ultrasound and magnetic resonance imaging features in a fetus with Walker-Warburg syndrome. Ultrasound Obstet Gynecol 2009 Mar;33(3): 363-365.
24. Stroustrup Smith A, Levine D, Barnes PD, Robertson RL. Magnetic resonance imaging of the kinked fetal brainstem: a sign of severe dysgenesis. J Ultrasound Med 2005 Dec;24(12):1697-1709.
25. Stutterd CA, Leventer RJ. Polymicrogyria: a common and heterogeneous malformation of cortical development. Am J Med Genet C Semin Med Genet 2014 Jun;166C(2):227-239.
26. Barkovich AJ. Current concepts of polymicrogyria. Neuroradiology 2010 Jun;52(6):479-487.
27. Kappou D, Chlapoutaki C, Papastefanou I, Theodorou G, Kassanos D, Souka AP. Second-trimester sonographic diagnosis of polymicrogyria. J Ultrasound Med 2016 Oct;35(10): 2296-2299
28. Dhombres F, Nahama-Allouche C, Gelot A, Jouannic JM, deVillemeur TB, Saint-Frison MH, le Pointe HD, Garel C. Prena-tal ultrasonographic diagnosis of polymicrogyria. Ultrasound Obstet Gynecol 2008 Dec;32(7):951–954.
29. Howe DT, Rankin J, Draper ES. Schizencephaly prevalence, prenatal diagnosis and clues to etiology: a register-based study. Ultrasound Obstet Gynecol 2012 Jan;39(1):75-82.
30. Vinurel N, Van Nieuwenhuyse A, Cagneaux M, Garel C, Quarello E, Brasseur M, Picone O, Ferry M, Gaucherand P, des Portes V, et al. Distortion of the anterior part of the interhemispheric fissure: significance and implications for prenatal diagnosis. Ultrasound Obstet Gynecol 2014 Mar;43(3):346-352.