Recent Fetal Neurology: From Neurosonography to Neurosonogenetics

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ABSTRACT

Among various congenital central nervous system (CNS) malformations, only cranial bifidum, spinal bifidum, and holoprosencephaly can be diagnosed during the early embryonic/fetal stage. Other CNS dysmorphic diseases occur after 13 weeks of gestation because CNS is formed through several developmental stages, including cell proliferation, neuronal migration, and post-migrational phases, after three gestational months. The recent significant advance of three-dimensional (3D) sonographic technology has accelerated fetal neuroimaging. Since the introduction of transvaginal, transfontanelle neuroimaging technique introduced in clinical practice, combined with 3D technology, has enabled us to conduct systematic neuroimaging analyses. Recently, congenital brain abnormalities have been classified not only by their morphological features but causal genetic factors. In this article, the author describes prenatal neuroimaging diagnoses and genetic causes, and fetal CNS disorders.

Keywords: Brain damage, Exome sequencing, Fetus, Malformations of cortical development, Migration, Neurology, Neurulation, Proliferation, Prosencephalic, Single gene mutation.

Donald School Journal of Ultrasound in Obstetrics and Gynecology (2021): 10.5005/jp-journals-10009-1718

INTRODUCTION

Neuronal embryology shows the rapid development of the central nervous system (CNS) during pregnancy. Various disorders due to genetic mutation, trauma, viral infection, and other factors, and unexpected events during developmental stages can result in multiple phenotypes of congenital CNS abnormalities. It is essential to know the congenital CNS diseases related to each developmental stage of the CNS, such as neurulation, prosencephalic development, cell proliferation, neuronal migration, organization, and myelination.

Most fetal abnormalities can be diagnosed in early pregnancy or during the first trimester due to recent advanced fetal ultrasound.1–3 However, it is challenging to detect brain malformations because the CNS structure is not accomplished in the early stage. The proliferation of neuronal cells, neuronal migration from the ganglionic eminence and ventricular zone (VZ) start from 3 months of gestation. The recent advance of three-dimensional (3D) ultrasound technology has enabled us to conduct precise prenatal neuroimaging as if it were postnatal magnetic resonance imaging (MRI). The transfontanelle neuroimaging procedure combined with the 3D ultrasound (Fig. 1) has been introduced. Systematic and accurate neuroimaging contributes to the detection of various congenital brain abnormalities, including the malformations of cortical development (MCD).

Cranial Dysraphism (Neurulation Disorder)

The neural tube is a single tubular structure from the head to the tail during development and is the primordium of the brain and spinal cord that constitutes the CNS. The neural tube is derived from the neural plate, which has a simple squamous epithelial structure. The formation of a vascular structure is initiated by forming a neural ridge near the boundary between the neural plate and the epidermal ectoderm and a neural groove in the middle of the neural plate. The actin cytoskeleton is abundant on the apical side of the neural epithelial cells that make up the neural plate, contracts, causing distortion in the neural plate and bending the neural plate. After that, the left and right ridges of the neural plate are fused, and the neural plate finally breaks from the epidermal ectoderm and changes to a tubular structure. Such a mode of development is called primary neurulation. On the other hand, in the tail of mammalian and avian embryos, neural tube formation is observed due to the epithelialization of mesoderm mesenchymal cells. This mode is called secondary neurulation.

It is known that over 200 genes in mice cause neural tube defects (NTDs). The phenotype pattern in humans is a multifactorial polygenic or oligogenic etiology.4,5 Acrania and anencephaly embryos, the complete/incomplete brain, and calvarial defects are found. The craniorachischisis is characterized by neural tissue exposure associated with both calvarial and spinal defects. Encephalocele was classified as one of the NTDs. It has been, however, controversial whether encephalocele is NTD or a post-neurulation defect. Rolo et al. used the mouse model experiment and described that the encephalocele is not the consequence of the failure of neural tube closure but rather due to a later disruption of the surface ectoderm which covers the already closed neural tube.6 Thus, the true pathogenesis of encephalocele remains unclear. The other considerable etiologies include single gene...
mutation, multifactorial inheritance, specific drugs such as valproic acid, and environmental factors. For a long time, it was thought that maternal serum alpha-fetoprotein level increases in NTDs. However, in skin-covered encephalocele or NTD fetuses, maternal serum alpha-fetoprotein level is normal. Therefore, neurosonography is a powerful tool for detecting NTDs during pregnancy.

Holoprosencephaly (Prosencephalic Disorder)

The incidence of holoprosencephalic infants is 1 out of 15,000 to 20,000 live births. However, it has been described that the initial incidence in aborted human embryos might be >60 times higher than the incidence of live births.7,8 Holoprosencephaly is classified into three varieties; alobar, semilobar, and lobar types. Seventy-five percent of holoprosencephalic individuals have no genetic cause identified; the rest are due to genetic factors. The most common chromosomal aberration is Trisomy 13. Several gene mutations were identified as genetic causes of holoprosencephaly, such as Sonic Hedgehog (SHH), located on 7q36, ZIC2 on 13q32, SIX3 on 2p21, and TGFβ on 18p11.3.7,9–12 In individuals with normal karyotypes, point mutations or pathogenic copy number variation, including those genes, are identified in approximately 22%.13 Approximately 80% are accompanied by facial abnormalities due to hypoplasia of the midline of the face, such as hypotelorism, cyclopia, nasal septum defect, proboscis, rhinoplasty, cleft lip, and palatoseptal adhesion molecule) gene is located on Xq28, the primarily male disorder. Patients affected by LICAM have severe disabilities such as mental retardation, spasticity of the lower limbs, and paralysis of the lower limbs, with features such as hydrocephalus with AOCC and adducted thumbs.

In some of the syndromes with AOCC, causative genes are not identified. Aicardi syndrome,30 featured by AOCC, infantile spasms, chorioretinal lacunae, etc., including coloboma and microphthalmia, is inherited with an X-linked dominant pattern and has a paired X chromosome. Therefore, the affected individuals are mostly females, although males with XXY karyotypes (Kleinfelter syndrome) can be affected. The prevalence is 0.63 per 100,000 females.31 Intrahemispheric cysts (Fig. 3) or pericallosal lipoma can be associated with AOCC.

Malformations of Cortical Development

The cortex of the brain is formed as a consequence of the complicated dynamic process. There are three stages of the process of cortical development.32 The first stage is the cell proliferation phase, in which baby neuronal cells increase in number and differentiate into neurons or glial cells in the subventricular zone (SVZ) and VZ. The second stage is the neuronal migration phase. The excitatory neurons are tangentially migrating toward the cerebral surface from the VZ/SVZ. This third stage is the organization phase, in which the six layers of the cortex are formed in an inside-out manner.33

As described above, it is obvious that the cerebral cortex is formed during the fetal period, and malformations of cortical development (MCD), dysplasia of the cerebral cortex, is a disease that is completed during the fetal period. However, MCD is rarely detected during the fetal period. Mostly, MCD is diagnosed after birth by MRI due to developmental delay or epilepsy, and then the causal factors are investigated by genetic examinations.34 Malformations of cortical development have been classified into three groups according to the three developmental stages described above, and >100 genes were identified as responsible for MCD. However, because MCD-related genes are involved in multiple developmental stages, it has been assumed that the tissues of proliferation, migration, and post-migration are genetically and functionally interdependent, it has turned out that it is difficult to classify MCDs into these three groups.35,36

Proliferation and Apoptosis Disorders

Microcephaly is classified as a proliferation disorder secondary to degeneration of normal growth and subsequent loss of neuronal
Microcephaly vera, actual microcephaly or primary microcephaly, results in intellectual disability after birth. Infants with microcephaly vera have no apparent brain malformations despite small brains. The phenotypes are not always uniform. There is a continuum between microcephaly with regular gyral formation and microcephaly associated with other malformation, such as microlissencephaly. The causal factors of microcephaly include fetal infections by rubella virus, cytomegalovirus (CMV), ZIKA virus and toxoplasmosis, and single-gene mutations. There are several responsible genes for microcephalies, such as Microcephalin (MCPH1), ASPM, CDK5RAP2, CENPJ, STIL, WDR62, and CEP152 and others. In the case of microcephaly, neurosonographic observation of the intracranial structure through the cranial fontanelle is often very difficult because the cranial sutures and fontanelle are very narrow due to microencephaly. For a detailed evaluation of intracranial structure in cases with microcephaly, MRI is highly recommended.

**Neuronal Migration Disorders**

On the brain surface, the gyri and sulci are detectable by neurosonogram after the late 7 months of gestation. The further gyral elaboration continues during the rest of fetal life and shortly after birth. Neuronal migration is controlled by a complicated series of chemical guidance and signals. If these signals are absent or incorrect, neuronal cells will not be able to reach where they should belong. Migration disorder is structurally abnormal or missing areas and occurs in any part of the intracranial structure, such as the cerebral hemispheres, brainstem, hippocampus, and cerebellum. Migration disorders include lissencephaly, agyria, pachygyria, microgyria, polymicrogyria, heterotopias such as periventricular nodular heterotopia and band heterotopia. These gyral developmental aberrations often cause seizures, epilepsy, and neurological deficits from early in life. Migration disorders are prominent in the cerebral cortex in late pregnancy. Therefore, it seems impossible to detect migration disorder at mid-gestation.

Figs 2A to D: Neurosonographic images of fetal holoprosencephaly: (A) The coronal tomographic ultrasound images. Note a fused ventricle between the left and right ventricles; (B) HDlive silhouette image of the fused ventricle; (C) HDflow image in the coronal section. MV, medullary veins; LSA, lenticulostriate arteries; (D) 3D surface image of the fetal face. Arrhinia and cleft lip are clearly demonstrated.
Lissencephaly is characterized as a cortical malformation associated with disorders of gyrus formation due to migration disorder. The spectrum of lissencephaly includes agryria, pachygyria, and subcortical band heterotopia. Lissencephaly was traditionally divided into two types. Lissencephaly type I was with a smooth cortex develops macroscopically during the second trimester, and regular gyrus pattern detected by transabdominal sonography. The Sylvian fissure development becomes one of the markers of cortical development resulted from normal migration. According to the development of the brain, the change in the appearance of Sylvian fissure is remarkable. Poon and the authors’ group proposed the Sylvian fissure angle indicating a significant increase as advancing gestational age. Furthermore, Pooh et al. showed 21 MCD cases among 22 between 18 weeks and 30 weeks of gestation, with the delayed development of the Sylvian fissure with a wider Sylvian angle than before gyrus formation, and revealed pathogenic genetic mutation or CNV in >30% of MCD cases.

Lissencephaly was traditionally divided into two types. Lissencephaly type I was with a smooth brain and type II with a cobblestone appearance. However, as many responsible genes for migration disorders were clarified thereafter, lissencephaly classification was changed depending on the pathogenesis and etiology. LIS1 mutation on 17p13.3, PAFAH1B1 gene mutation, subdivided into Miller–Dieker syndrome, and lissencephaly due to doublecortin mutation was into DCX mutation group. Cobblestone lissencephaly includes muscle–eye–brain disease (MEB) due to POMGnT1, Walker–Warburg syndrome due to POMT1, POMT2, CRPPA, FKTN, FKRP, and LARGE1, and Fukuyama syndrome due to Fukutin. ARX gene on Xq22.1 is another lissencephaly. Reelin gene on 7q22.1 causes Norman–Roberts syndrome, and microlissencephaly.

Thus, with recent rapid advances in molecular genetics, a conventional classification system became inadequate to distinguish various patterns of lissencephaly to predict the most likely causative gene mutations; a new classification based on imaging was proposed in 2017. Several reports on the prenatal diagnosis of lissencephaly have been published.

Post-migrational Disorders

Polymicrogyria is the most common MCD relate post-migrational cause. Copy number variations of 1p36.3 deletion, 22q11.2 deletion, and mechanistic target of rapamycin (mTOR)-related genes are often associated with polymicrogyria and macrocephaly. Germline mutations that affect the PI3K/AKT/mTOR pathway are involved in certain hereditary diseases. The loss of the tumor suppressor phosphatase tensin homolog (PTEN) causes congenital diseases, such as Cowden syndrome, Bannayan–Riley–Ruvalcaba syndrome, PTEN-related proteus syndrome, and proteus-like syndrome. The author and colleagues recently reported a rare case with megalencephaly with cortical maldevelopment due to PTEN mutation, as shown in Figure 4.

Peri-sylvian bilateral polymicrogyria is often associated with schizencephaly. Schizencephaly is characterized by congenital cerebral clefts, lined by pial–ependyma, with communication between the subarachnoid space laterally and the lateral ventricles medially. Schizencephaly occurs unilaterally in 63 and 37% bilaterally. A considerable cause is a vascular disruption during cortical development, genetic factors such as WDR62 mutation, which causes schizencephaly as well as microcephaly, indicating relations between processes of proliferation and schizencephaly pathogenesis, and COL4A1 mutation.

Ventriculomegaly

Ventriculomegaly is defined when an atrial width diameter is measured 10 mm or higher. Ventriculomegaly during fetal life is categorized into mild (10–12 mm), moderate (13–15 mm), or severe (>15 mm) types. The incidence of mild to moderate type is approximately 1%. Mild ventriculomegaly seems to be a normal variant if other associated abnormalities do not exist, and genetic exam is normal.

Hydrocephalus and ventriculomegaly are the terms that indicate the pathological condition with enlarged lateral ventricles. Hydrocephalus is mainly associated with increased intracranial pressure (ICP) by obstruction or stenosis of cerebrospinal fluid (CSF) flow pathway, and neurosonography reveals dangling choroid plexus inside the enlarged ventricles. On the other hand, normal-pressure hydrocephalus (NPH) is associated with enlarged ventricles without increased ICP, and with the normal appearance of choroid plexus. Hydrocephalus commonly occurs due to congenital stenosis of the cerebral aqueduct stenosis. However, secondary ventriculomegaly can occur due to vascular disease, intracranial tumor, or cysts, intracerebral or intraventricular hemorrhage (IVH), cortical maldevelopment, meningitis, Chiari malformation due to myelomeningocele, encephalopathy, and other CNS disorders. The causal factors of hydrocephalus and ventriculomegaly vary widely: neuronal adhesion, vesicle trafficking, dystroglycanopathies, ciliopathies, RASopathies, planar cell polarity, and NTDs, lysosomal storage disorders, growth factors, Wnt signaling pathway, PI3K/AKT/mTOR pathway to transcription factors.

Owing to recent genetic sequencing technologies, four well-known genetic mutations have emerged as causes of congenital hydrocephalus: L1CAM, AP152 (X-linked) and CCDC88C, MPDZ (autosomal recessive). Furthermore, over 100 genes were identified as the genetic causal factors of genetic hydrocephalus or ventriculomegaly.
cell–cell adhesion, the guidance of neurite outgrowth, bundling, myelination, and pathfinding, long-term potentiation, neuronal cell survival, migration, and synaptogenesis.\(^93\) Mutated \(L1CAM\) results in invariable neurological phenotypes, such as hydrocephalus, AOCC or HOCC, and adducted thumbs (Fig. 5). Because of X-linked recessive inheritance, the carrier mother’s male fetus has a 50% chance of being affected.

The CSF flow is also affected by asynchronism or abnormal beating of the ependymal cilia lining the ventricular system. Therefore, ciliopathies such as Bardet–Biedl syndrome (mutation of \(CEP290\)^94), Meckel syndromes (mutations of \(MKS1, TMEM6^95–97\), and Joubert syndromes (mutations of \(TMEM216^98,99\) \(CC2D2A^100\) and other genes) are often associated with ventriculomegaly.

Muscular dystrophies occur due to the aberrant glycosylation of \(\alpha\)-dystroglycan and are collectively termed dystroglycanopathies.\(^89,101\) Dystroglycanopathies often cause brain and ocular pathology. In cases of dystroglycanopathy, a disorder of neuronal cell migration results in cortical disorders and subsequent ventricular enlargement. Walker–Warburg syndrome (\(POMT1, PONT2,\) and \(B3GALNT2\)), MEB (\(POMGnT1\)), and Fukuyama congenital muscular dystrophy (\(FKTN\)) are representative dystroglycanopathies.

**Figs 4A to C:** Neurosonographic images and the schematic illustration of the fetus’s genetic events with \(PTEN\) mutation on paternal UPD 10q mosaicism.\(^78\) (A) Neuroimaging at 18th gestational week. Macrocephaly with asymmetrical megalencephaly due to \(PTEN\) mutation. Arrows indicate the persistence of ganglionic eminence, abnormal sulcation, and the irregular ventricular wall; (B) Neuroimaging at 20th week. From left, anterior coronal, posterior coronal, and parasagittal views. Sonogram depicted the remarkable polygyria that were not seen in the 18th week; (C) Schematic illustration of genetic events
**PI3K/AKT/mTOR** pathway-related genes are identified in several other overgrowth syndromes. The megalencephaly-polymicrogyria-polydactyly-hydrocephalus syndrome (MPPH) and megalencephaly-capillary malformation-polymicrogyria syndromes (MCAP) are spectrums of megalencephaly-associated syndromes characterized by megalencephaly, polymicrogyria, ventriculomegaly, and Chiari Malformation. In megalencephaly-associated syndromes, the mechanisms of ventriculomegaly is that megalencephaly induces polymicrogyria and cerebellar overgrowth, leading to oppression of the posterior fossa cerebellar tonsillar herniation, which eventually obstructs CSF flow. However, as Chiari malformation does not always exist, CSF flow obstruction may occur within the overgrown brain.

Mutations of growth factors related to genes such as FGFR3 can lead to skeletal dysplasia (Thanatophoric dysplasia) with enlarged ventricles associated with overgrown and hyper-convoluted temporal lobe, as shown in Figure 6.

The term “Isolated” ventriculomegaly is often used when no other brain abnormalities and extra-CNS anomalies are found. However, in many “antenatally isolated” ventriculomegaly cases, extra-CNS abnormalities, other CNS disorders, and single-gene mutation are often found after birth. Detailed observation of ventricular shapes, intracerebral and extra-CNS morphology may lead to identifying causal factors and prognostic evaluation far more than evaluation from AW measurement only. To find out causes of enlarged ventricles, chromosomal microarray, targeted/whole-exome sequencing, or whole-genome sequencing, as well as viral antibody analysis, may be recommendable. Furthermore, longitudinal study during the fetal period by neurosonography is essential because the spontaneous resolution of enlargement during pregnancy is seen in some isolated ventriculomegaly cases.

**In utero Brain Injury and Damage**

In neonates with encephalopathy and cerebral palsy, “When causal event occurred, antepartum, intrapartum or postpartum?” is a critical question because it involves medico-socio-legal-ethical issues. Brain insults are probably associated with antenatal events such as single gene disorder, high cardiac output, encephalopathy due to various factors, as shown in Figure 7. It is not always possible to specify when the event occurred. The causative events for encephalopathy may be occasionally speculated, e.g., selective intrauterine fetal death (sIUDF) or fetal intervention for twin-to-twin transfusion syndrome in cases of monochorionic twins. However, it is challenging to grasp prenatal evidence of in utero brain injury, which causes postnatal neurological deficits. Neurosonography and neuro-MRI are reliable modalities for detecting silent encephalopathy.

In many cases with cerebral palsy, there might be in utero brain insults. Term-delivered infants with re-assuring fetal heart rate monitoring at delivery are not suspected of having brain damage or injury. Therefore, it is hard to identify the exact incidence. Fetal intracranial bleeding is a rare condition and has been called a fetal stroke after 2004 and other various descriptions were used in published reports, such as fetal cerebrovascular disorder or perinatal brain injury. Fetal stroke is an event between the 14th week and labor onset and cited an incidence of about 17 to 35 of 100,000 live births, or 0.5 to 1.0/1,000 pregnancies. In a report in 1985, a series of stillbirth autopsies showed 6% with the evidence of fetal intracranial hemorrhage. Various causal factors of fetal intracranial bleeding or hemorrhage are considered, including idiopathic, alterations of fetal blood pressure, placental abnormalities, umbilical vascular abnormalities, trauma, fetomaternal hemorrhage, fetal infection, single-gene mutations, allogeneic and idiopathic
thrombocytopenia, von Willebrand’s disease, illicit drug (cocaine) abuse or specific medications (warfarin), twin-to-twin transfusion, congenital factor X deficiency, factor-V deficiency, vascular diseases, and intracranial tumor, and the sIUFD of monochorionic twin. COL4A1 and COL42A gene mutations are strongly associated with perinatal cerebral bleeding and porencephaly.\(^{111-117}\) Fetal neuroimaging demonstrates hyperechoic lined ventricular wall, avascular intracranial mass, porencephalic cysts, parenchymal echogenicity, hyperechoic acute clot adherent to choroid plexus, increased periventricular white matter echogenicity, and hyperechoic nodular ependyma, which are often demonstrated in cases with cerebral bleeding. Secondary ventriculomegaly often occurs because of the Monro stenosis or obstruction by blood clots.

The definition of primary IVH, when intraventricular events such as choroid plexus tumor or bleeding are apparent. The incidence of primary IVH is approximately 30%, and the rest 70% is secondary IVH. The most common cause of secondary IVH is intraparenchymal bleeding, expanding into the ventricular system. The infantile IVH grading was first reported by Papile et al.\(^{118}\) Grade I is isolated to the periventricular (subependymal) germinat matrix, Grade II

Figs 6A to D: *FGFR3*-related thanatophoric dysplasia with ventriculomegaly associated with overgrown and hyperconvoluted temporal lobe: (A) Neurosonographic image in the parasagittal fetal brain at 16 weeks. Note the serpentine appearance of the overgrown brain parenchyma; (B) Neurosonographic image in the posterior coronal fetal brain at 16 weeks; (C) Power Doppler image in the parasagittal section. The superficial cerebral vessels run along the serpentine-shaped cerebrum; (D) The autopsy findings at 21 weeks. The view from the basilar. Note the abnormal sulci of the cerebri

Figs 7A to D: In utero brain injury due to various causal factors: (A) Intracranial bleeding with porencephalic change due to COL4A1 gene mutation; (B) Bilateral multiple intracranial hemorrhages are seen in a hydropic fetus. The cause might be the increased cardiac output due to congenital heart disease; (C) Destructive encephalopathy after sIUFD of monochorionic twin; (D) Cerebral hemorrhage with ventriculomegaly. The causal factor was uncertain
imply IVH (10–50%) without ventricular dilatation, Grade III is IVH (>50% or with ventriculomegaly), and Grade IV is with parenchymal hemorrhage or periventricular hemorrhagic infarction.119

Future Perspective
As shown in this article, the recent advances in 3D neurosonography have enabled us the systematic evaluation of fetal brain morphology. Owing to the rapid advances of molecular genetics, >100 genes have been identified as responsible mutations for congenital cortical abnormalities. Most congenital CNS disorders are deeply involved with developmental stages, genetic causes, environmental factors, and intrauterine events. Prenatal counseling for parents was conducted according to a morphology-based diagnosis. Nowadays, however, as CNS diagnoses can be made, detailed neuroimaging, genetic examination of chromosomal microarray, exome sequencing, and genome sequencing adds causal genetic factors. Prenatal genetic counseling in cases with congenital brain abnormalities is done according to all those results. Detailed neurosonography combined with molecular genetics has established "Neuro-sono-genetics", a new field in multidisciplinary fetal neurology, for proper perinatal management and care, and future treatment and prevention.120,121

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