**Fetal Brain Structure and CNS Anomalies**

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**Abstract**

As the brain is an organ that must be understood as a three-dimensional (3D) structure, and because the fetal skull ossifies in late pregnancy, it is difficult to depict detailed structures in the brain using conventional horizontal cross-sectional images captured by transabdominal ultrasound. However, there are large spaces such as anterior/posterior fontanels and sagittal sutures in the fetal skull. By using these spaces as a window for ultrasound, it becomes easier to observe the brain structure. Transvaginal fetal 3D neurosonography and transvaginal ultrasound have made it possible to observe congenital brain structural abnormalities and cortical dysgenesis in more detail. Transvaginal 3D ultrasound imaging has been reported to be effective in the evaluation of fetal brain structure. Images of normal brain development, intracerebral vascular architecture, brain malformations, brain disorders such as intracerebral hemorrhage and stroke, and abnormalities in cortical development have gradually revealed the previously unknown development and pathology of the fetal brain. Fetal 3D neurosonography provides information on the orientation of the fetal brain, brain development during pregnancy, the exact location of brain lesions, and the inner structure of the lesions. Detailed neuroimaging is now available for diagnosis of the central nervous system, and genetic tests such as chromosomal microarrays, exome sequencing, and genome sequencing add information on genetic causative factors. The combination of detailed neurosonography and molecular genetics has established a new interdisciplinary field of fetal neurology called “neurosonogenetics,” which will enable accurate perinatal management and care in the future.

**Keywords:** Fetal brain, Molecular genetics, Three-dimensional neurosonography, Transvaginal ultrasound.

**Introduction**

Because the brain is an organ that must be understood as a 3D structure, and because the fetal skull ossifies in late pregnancy, it is difficult to depict detailed structures in the brain using conventional horizontal cross-sectional images captured by transabdominal ultrasound. However, there are large spaces such as anterior/posterior fontanels and sagittal sutures in the fetal skull. By using these spaces as a window for ultrasound, it becomes easier to observe the brain structure. Transvaginal ultrasound observation of the fetal brain began in the 1990s,¹ and the combination of fetal 3D neurosonography and transvaginal ultrasound has made it possible to observe congenital brain structural abnormalities and cortical dysgenesis in more detail. Transvaginal 3D ultrasound imaging has been reported to be effective in the evaluation of fetal brain structure.²⁻⁷ Images of normal brain development, intracerebral vascular architecture, brain malformations, brain disorders such as intracerebral hemorrhage and stroke, and abnormalities in cortical development have gradually revealed the previously unknown development and pathology of the fetal brain. This chapter comprehensively illustrates how to observe the fetal brain using 3D ultrasound, imaging, and genetic diagnosis of brain lesions.

**How to Obtain Orientation by 3D Neurosonography?**

When the fetus is in the pelvic or lateral position, the head of the fetus is located at various sites inside the uterus, and neuroimaging can be obtained by the transabdominal incidence of ultrasound beam from the fontanels or sagittal suture. In the case of a fetus in the cephalic position, the presence of the maternal pubic bone makes it difficult to approach the fetus from the top of the head with transabdominal ultrasound. Therefore, if the fetus can be externally rotated to the pelvic position of the fetal head can be manually pushed upwards, it will be easier to...
observe the intracranial structures by the transabdominal method. However, transvaginal ultrasound allows us to use a transvaginal probe with higher resolution than the transabdominal probe without interference from the maternal abdominal wall or placenta, allowing us to observe the brain in great detail. The difficulty with transvaginal ultrasonography is positioning the fetal head so that the anterior fontanelle or sagittal suture is located at the tip of the probe. Once the position is adjusted, the region of interest (ROI) and the angle of the scan width is determined, and the automatic scan is started (Fig. 1).

After acquiring the images, an offline analysis is performed. When observing the fetal brain with transvaginal ultrasound, unlike transabdominal ultrasound, it is difficult to align the orientation of the left and right brain hemispheres. The solution to this problem lies in the manipulation of 3D images. First, three orthogonal views A, B, and C, are displayed. Image A shows a coronal section of the brain, B shows a sagittal section, and C shows a horizontal section. It is important to note that in B, the anterior part of the brain is located on the left side of the screen. In coronal section A, the left side of the fetal brain is depicted on the right side of the screen and the right side of the fetal brain is on the left side of the screen (Fig. 2).  

By obtaining the left and right orientation of the fetus, it is possible to clearly identify which hemisphere has the asymmetric lesion. This method is currently not universal, but if you follow these rules, you can get the orientation of the brain quite easily, especially in cases with asymmetrical brain structures.

Fig. 1: Illustration of transvaginal 3D neurosonography. (Left) Transvaginal neurosonography. Transvaginal ultrasound can provide a very detailed view of the brain without the interference of the maternal abdominal wall or placenta. (Right) Once the position is adjusted, the region of interest (ROI) and the angle of scan width are determined, and the automatic scan is started.
**Observation in Tomographic Imaging**

Similar to magnetic resonance imaging (MRI) and computed tomography (CT), tomographic ultrasound imaging (TUI) can be used to produce slice images parallel to each plane. This is a very comprehensive imaging method not only for obstetricians but also for pediatric neurologists and pediatric neurosurgeons. The slice width can be easily changed in TUI to view parallel slice images of the brain. Similarly, in the TUI image, the brain image itself can be moved, keeping the slice width constant, to view a series of parallel slice images. In comparison to MRI and CT in terms of offline analysis, 3D neurosonography has the advantage of being able to view a continuous cross-section of the brain with different slice widths (Fig. 3).

**Application and Advantages of 3D Neurosonographic Image**

A variety of 3D representations are available for 3D ultrasound images, including three orthogonal views, TUI, inverted image, HDlive silhouette ultrasound, thick-slice silhouette image, and volume-cutting image (Fig. 4). Silhouette ultrasound imaging is a recent advanced 3D technique that creates gradients in the walls of fluid-filled cavities and vascular walls where rapid changes in acoustic impedance occur.10–17 The HDlive silhouette mode displays fluid-filled cystic structures through the outer surface structures, and in prenatal images, the image is “see-through.”15 to depict the ventricular system, including the lateral and third ventricles, along with the outer surface of the cranium. A thick slice silhouette image is created by cropping the volume data in a rectangular shape and rendering it using the silhouette method.

What makes 3D neurosonographic imaging so useful in clinical practice is the ability to longitudinally compare brain structures that change during pregnancy in the exact same section of the same case. Another major clinical advantage of 3D neurosonographic imaging is the ability to compare abnormal brain structures with normal brains in the exact same cut section at the exact same gestational week. The comparison between abnormal and normal is very common and useful in clinical practice.

**3D Ultrasound Intracranial Angiography**

Combining transvaginal 3D ultrasonography with color Doppler and power Doppler has enabled advanced evaluation of fetal brain development and cerebral blood flow. The author reported transvaginal 2D power Doppler angiography in the first trimester in 1996.18 Since then, 3D power Doppler angiography has provided greater detail of the main cerebral arteries, dural sinuses, and fine peripheral vessels.19,20 Another recent technology, HDlive flow, has enabled 3D visualization of blood flow and microvasculature (Fig. 5); the combination of HDlive silhouette and HDlive flow provides a comprehensive orientation of intracranial vascular structures and confirms the location of vascular trajectories within morphological structures.21

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Figs 3A to D: Tomographic ultrasound imaging (TUI) with changing slice width. The slice width can be easily changed from A to B to view parallel slice images (C and D) of the brain.
The neural tube originates from the neural plate, which has a simple flattened epithelial structure. A neural ridge is formed near the boundary between the neural plate and the epidermal ectoderm, and a neural groove is formed in the middle of the neural plate. The actin cytoskeleton, which is highly concentrated on the apical side of the neuroepithelial cells, makes up the neural plate, and contracts causing the neural plate distortion and bending of the neural plate. Later, the left and right sides of the neural plate fuse, and the neural plate finally changes from epidermal ectoderm to a tubular structure. This developmental pattern is called primary

In addition, the recent advanced technology of 3D Slowflow has made it possible to visualize these vascular structures in more sophisticated 3D, and fine intracerebral vessels such as lenticular arteries and medullary veins can now be depicted even more clearly (Fig. 6). These innovations make it possible to easily grasp the vascular structure of the entire brain.

Cranial Dysraphism (Neurulation Disorder)

A neural tube is a single tubular structure that runs from head to tail during development. It is the original basis for the brain and spinal cord that make up the central nervous system. The neural tube originates from the neural plate, which has a simple flattened epithelial structure. A neural ridge is formed near the boundary between the neural plate and the epidermal ectoderm, and a neural groove is formed in the middle of the neural plate. The actin cytoskeleton, which is highly concentrated on the apical side of the neuroepithelial cells, makes up the neural plate, and contracts causing the neural plate distortion and bending of the neural plate. Later, the left and right sides of the neural plate fuse, and the neural plate finally changes from epidermal ectoderm to a tubular structure. This developmental pattern is called primary
bifida, such as myelomeningocele (Fig. 7) and meningocele is a typical NTD, and Chiari type II causes herniation of the cerebellar tonsils and medulla oblongata into the spinal canal, resulting in narrowing of the 4th ventricle and midbrain aqueduct, and consequently ventricular dilatation. In the case of enlarged ventricles associated with Chiari malformation, the enlarged ventricles have a characteristic angular or triangular shape due to intracranial negative pressure (Fig. 8). The etiology of encephaloceles is not well apprehended. It has been classified as an NTD; however, it’s controversial if the encephalocele is an NTD or a post-neurulation defect;

neurulation. Meanwhile, in the caudal part of mammalian and avian embryos, neural tube formation by epithelialization of mesodermal mesenchymal cells is observed, and such a mode is called secondary neurulation.

In mice, there are >200 genes that are known to cause NTDs - neural tube defects. In humans, the developmental pattern is found to be multifactorial, polygenic, or oligogenic in etiology. In acranial-anencephalic embryos, one can see a complete or incomplete loss of brain tissue and cranium. Craniorachischisis is characterized by anencephaly with continuous spinal cord defects and exposed neural tissue. Spina bifida, such as myelomeningocele (Fig. 7) and meningocele is a typical NTD, and Chiari type II causes herniation of the cerebellar tonsils and medulla oblongata into the spinal canal, resulting in narrowing of the 4th ventricle and midbrain aqueduct, and consequently ventricular dilatation. In the case of enlarged ventricles associated with Chiari malformation, the enlarged ventricles have a characteristic angular or triangular shape due to intracranial negative pressure (Fig. 8). The etiology of encephaloceles is not well apprehended. It has been classified as an NTD; however, it’s controversial if the encephalocele is an NTD or a post-neurulation defect;
karyotypes, point mutations or pathogenic copy number changes involving these genes have been identified. About 80% of cases are associated with facial abnormalities such as hypotelorism, cyclopia, arrhinia, proboscis, cleft lip, and palate due to hypoplasia of the midline of the face. Figure 9 shows semilobar holoprosencephaly at 16 weeks of gestation.

Agenesis of the Corpus Callosum
The most extensive fiber bundle structure in the cerebrum is the corpus callosum (CC) which connects the left and right cerebral hemispheres, integrating sensory and motor information, and is associated with higher cognition. The FGFR8 is an essential gene for the early forebrain patterning and formation of the commissural plate; ZIC2, NFIA, EMX1, and SIX3 are genes responsible for the development of the CC, hippocampus, and anterior commissure. The final form of the CC is completed by the 20th week after conception, but axonal growth continues after birth. Even though CCs are not formed during the early stages of central nervous system development, early cerebral events are essential for CC formation, including the coupling of morphogenetic gradients with the development of thalamocortical circuits are essential to forming the CC.

Agenesis of the Corpus Callosum (AOCC) is a brain malformation that occurs in isolation or in association with asymptomatic disease. AOCC includes complete AOCC (meaning the absence of CC completely, you can see it in Figure 10), partial AOCC, and hypoplastic CC with...
Fig. 9: Semilobar holoprosencephaly at 16 weeks. Tomographic ultrasound imaging on coronal plane. Note the fused single ventricle.

Figs 10A to D: Agenesis of the corpus callosum at 18 weeks. (A) Mid-sagittal section. The corpus callosum is not visualized. (B) Coronal section. This particular case was associated with severe ventriculomegaly. (C) 2D sonoangiography shows the abnormal vascular direction of the pericallosal artery and its branches. (D) 3D sonoangiography provides more vascular information.
normal anterior to a posterior extent. Development of the CC is deeply related to the proliferation of the glial cell, midline patterning, migration of CC, specification, axon guidance, and postguidance steps, 32 1q42-q44 deletion, 35,36 4p16.3 deletion (Wolf-Hirschhorn syndrome), 37 8p rearrangements 38-40 17p13, 3 deletions (Miller-Dieker lissencephaly syndrome)41,42 and various other copy number mutations have been implicated in CC.

Mutations in the ARX gene 43–46 result in X-linked lissencephaly with absent corpus callosum and abnormal genitalia (XLAG), while mutations in L1CAM cause the L1 syndrome. Since an L1CAM (L1 cell adhesion molecule) gene is located on Xq28; the primarily male baby is affected. L1 is an essential gene for neuronal adhesion. L1CAM-affected patients have severe disorders with mental retardation, lower limb spasticity, and paraplegia.

In some syndromes associated with AOCC, the causative gene has not been identified. Aicardi syndrome, which is characterized by AOCC, infantile seizures, microphthalmia, and choroidal retinal tearing such as coloboma, 48 most of the affected individuals are females with two X chromosomes, and thus the gene has not been identified, but X-linked dominantly inherited. The age-adjusted prevalence is 0.63 per 100,000 women. 49 However, males with two X chromosomes (XXY, Klinefelter syndrome) may be affected. We can associate interhemispheric cysts (Fig. 11) or pericallosal lipomas with AOCC.

Malformations of Cortical Development (MCD)

The cerebral cortex is developed in a complex dynamic process. There are three stages in the formation of the cerebral cortex. 50 Cell proliferation stage is the first stage, in which stem cells increase in the ventricular zone (VZ) and subventricular zone (SVZ) and differentiate into neurons and glial cells, as well as programmed cell apoptosis. The second is the stage of neuronal migration. Neurons migrate tangentially toward the cortical plate, via the intermediate zone and subplate (Fig. 12), from the ventricular surface in an inside-out mode. This third is the organization stage, which forms the six layers of the cerebral cortex. 51

Thus, during the fetal period, the cerebral cortex is gradually formed and MCD is a disease completed during the fetal period. However, we cannot often detect MCD. During the fetal period, and in most cases, it is discovered after birth by a detailed examination such as MRI due to developmental delay or epilepsy, followed by genetic testing to determine

Fig. 11: Interhemispheric cysts associated with agenesis of the corpus callosum at 25 weeks. (Left) Coronal section. (Right) Mid-sagittal section

Fig. 12: Subventricular zone. Intermediate zone and subplate. Neurosonogram demonstrates the layers of subventricular zone (SVZ), intermediate zone (IMZ) and subplate (SP) clearly
after birth. In microcephaly vera, there is no obvious brain malformation and the phenotype is not always uniform. There is a continuum between microcephaly with regular gyrus formation and microcephaly with other malformations\textsuperscript{56-58} such as microlissencephaly. Causal factors for microcephaly also include prenatal infection with cytomegalovirus (CMV), Zika virus, rubella virus, and toxoplasmosis, as well as mutations in single genes. Genes responsible for microcephaly include Microcephalin (\textit{MCPH1}\textsuperscript{57,59,60}, \textit{ASPM}\textsuperscript{61}, \textit{CDK5RAP2}\textsuperscript{62}, \textit{CENPJ}\textsuperscript{52,62,63}, \textit{STIL}\textsuperscript{58,63}, \textit{WDR62}\textsuperscript{56,58,64,65}, and \textit{CEP152}\textsuperscript{66} and others. In most cases of microcephaly, it is extremely challenging to observe intracranial structures by neurosonography through the cranial fontanelle because the cranial fontanelle and sutures are very narrow due to the microcephaly. MRI is advisable for the detailed assessment of intracranial structures in cases of microcephaly.

On the surface of the brain, the brain gyri and sulci can be detected on neurosonograms after the second half of the seventh month of pregnancy. During the rest of the fetal period and shortly after birth, further development of the gyrus continues. Neuronal migration is controlled by a series of complex chemical guidance and signals. When these signals are not proper or are missing, the nerve cells fail to reach the place where they should properly belong. As a result, structural abnormalities or defects can occur in any part of the intracranial structure, including the cerebral hemispheres, cerebellum, hippocampus, and brain stem. Disorders of neuronal migration include agyria, pachgyria, lissencephaly (Fig. 13), polygyria (Fig. 14), polymicrogyria, neuronal heterotopias like periventricular nodular heterotopia (Fig. 15), and band heterotopia. From early in life, developmental abnormalities in gyration often lead to seizures and neurological dysfunction, while migration disorders become prominent in the cortex in late pregnancy. Toi and colleagues\textsuperscript{67} showed a regular pattern of gyration identified by transabdominal ultrasonography. The cerebral cortex develops after 18 weeks in the second trimester of pregnancy, and the most obvious change on neuroimaging

Figs 13A to D: Lissencephaly during pregnancy. (A) Coronal view at 23 weeks. Sylvian fissures are extremely premature. (B) Coronal view at 25 weeks. 23–25 gestational weeks is a time of great change in brain morphology, but in this case there is little change (C) Coronal MR image at 36 weeks. No gyral formation is seen. The appearance of sylvian fissure is almost the same as in 23 weeks. (D) Axial MR image at 36 weeks

Fig. 14: Asymmetrical polygyria at 28 weeks. (Left) one slice of coronal cutting section. Asymmetrical polygyria (arrowheads) is seen. (Right) MR image of the same case. Asymmetry, ventriculomegaly and premature sylvian fissure is clearly depicted by both neurosonogram and MRI
is the morphological change in the Sylvian fissure, and a link between the morphology of the Sylvian fissure and cortical dysplasia has recently been reported. In accordance with the development of the brain, remarkable change in the appearance of Sylvian fissure is noted. Poon et al. proposed the Sylvian fissure angle explaining a significant angle decrease as the gestational age progressed. Furthermore, Pooh et al. showed 22 MCD cases between 18 and 30 weeks gestation, with the delayed development of the Sylvian fissure with a wider Sylvian fissure angle than normal cases. Figure 16 compares Sylvian fissure appearance in the same cross-sections at the same gestational age between normal cases and MCD cases.

Lissencephaly is characterized as a malformation of the cerebral cortex with abnormalities in brain gyrus formation due to impaired neuronal migration. The spectrum of lissencephaly contains agyria, pachygyria, and subcortical band heterotopia. Conventionally, lissencephaly has been divided into two subtypes. Type I lissencephaly was characterized by a smooth brain, and type II lissencephaly characterized by cobblestone appearance. However, due to the recent rapid advances in molecular genetics, a conventional classification system has shown to be inadequate to distinguish various patterns of lissencephaly to predict the most likely causative gene mutations. In 2017 a new classification based on imaging was proposed. There have been published several reports on the prenatal diagnosis of lissencephaly. LIS1 on 17p13.3, PAFAH1B1 gene mutation, which subdivides into Miller-Dieker syndrome, and lissencephaly due to doublecortin (DCX) mutation. Cobblestone lissencephaly was subdivided; Muscle-eye-brain disease (MEB), Walker-Warburg syndrome due to POMGnT1, Fukuyama syndrome due to Fukutin, ARX

Fig. 15: Periventricular nodular heterotopia at 22 weeks. Parasagittal cutting section. Note the irregular hyperechoic nodules (arrowheads) are visualized along with a ventricular wall

Fig. 16: Comparison of Sylvian fissure appearance in the same cross-section at the same gestational age in normal fetuses and MCD cases. In MCD cases (lower), sylvian fissure (arrowheads) appearance is extremely premature, compared with normal cases (upper)
gene on Xq22.1\(^{31-86}\) mutation causes X-linked lissencephaly. *Reelin* gene on 7q22.1\(^{87-89}\) causes Norman-Roberts syndrome and microlissencephaly.\(^{53,91-95}\)

Polymicrogyria is the most common MCD associated with post-migration etiology. 1p36.3 deletion, 22q11.2 deletion, and copy number mutations in genes related to the mechanistic target of the rapamycin (mTOR) pathway are frequently associated with polymicrogyria, hemimegalencephaly, and macrocephaly. In certain inherited diseases, germline mutations affecting the PI3K / AKT / mTOR pathway have been implicated in the tumor suppressor phosphatase tensin homolog (PTEN) are found to cause congenital diseases like Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome, PTEN-associated Proteus syndrome, as well as Proteus-like syndrome. Recently, the authors reported a rare case of megalencephaly with cortical abnormalities caused by a PTEN mutation.\(^{96}\)

Schizencephaly is characterized by congenital cerebral clefts, lined by pial-ependyma, with communication between the subarachnoid space laterally and the lateral ventricles medially. Unilaterally Schizencephaly occurs in 63%, and bilaterally it occurs in 37%. Vascular disruption during corticogenesis is a considerable cause, genetic factors like *WDR62*, mutation\(^{56,58}\) which causes schizencephaly as well as microcephaly,\(^{64,65}\) indicating relations between processes of proliferation and schizencephaly pathogenesis, and *COL4A1* mutation\(^{97-100}\) Peri-sylvian bilateral polymicrogyria\(^{101-102}\) is also associated with schizencephaly.

![Fig. 17: L1 syndrome at 21 weeks. (Upper image) Tomographic ultrasound image in the sagittal section. Severe ventriculomegaly is seen. (Lower left) 3D image of fetal hand. The adducted thumb is clearly visualized. (Lower right) the adducted thumb of aborted fetus](image-url)
ventricular dilatation: dilatation of the lateral ventricles and third ventricle due to obstruction or stenosis of the pathways of the cerebrospinal fluid flow, resulting in increased intracranial pressure;\textsuperscript{104} and ventricular dilatation with normal intracranial pressure due to cerebral ramus defect.

**Ventriculomegaly**

Fetal ventriculomegaly is a condition in which the ventricles of the fetal brain are enlarged, and it is the most common brain abnormality detected by prenatal ultrasound, with an incidence of about 1\%.\textsuperscript{103} There are essentially two types of ventricular dilatation: dilatation of the lateral ventricles and third ventricle due to obstruction or stenosis of the pathways of the cerebrospinal fluid flow, resulting in increased intracranial pressure;\textsuperscript{104} and ventricular dilatation with normal intracranial pressure due to cerebral ramus defect.
Fetal ventricular enlargement is defined as an atrial width (AW) of 10 mm or more, which was defined in 1988, and remains constant regardless of the gestational age. The AW of less than 10 mm has been classified as normal, 10–15 mm as mild to moderate, and more than 15 mm as severely enlarged ventricles and various outcomes and prognoses have been reported depending on the classification. Terms hydrocephalus and ventriculomegaly indicate the pathological condition with enlarged lateral ventricles. Hydrocephalus is primarily associated with increased intracranial pressure (ICP) by occlusion or stenosis of cerebrospinal fluid (CSF) flow pathway and dangling choroid plexus inside the enlarged ventricles is revealed by neuroimaging. In contrast, normal-pressure hydrocephalus (NPH) is associated with enlarged ventricles without increased ICP, with the normal appearance of choroid or cerebral dysplasia. In some cases, temporary ventricular enlargement may occur and then resolve spontaneously.

The underlying etiologies of ventricular enlargement may include chromosomal abnormalities, microchromosomal abnormalities, genetic mutations, central nervous system developmental abnormalities, intracranial hemorrhage, neoplastic lesions, hypoxic brain injury, viral infections, and metabolic diseases. The neurological prognosis of ventriculomegaly is varied and diverse, ranging from very good to severe disability. The neurological prognosis is diverse and varied, ranging from very good to severe disability. Therefore, if ventricular enlargement is suspected, detailed fetal neurosonography, systemic examination, genetic testing, testing for infections, and follow-up for ventricular enlargement are necessary.

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plexus. Hydrocephalus generally occurs because of congenital stenosis of the cerebral aqueduct stenosis. However, secondary ventriculomegaly can occur because of vascular disease, cortical maldevelopment, intracranial tumor, or cysts, intracerebral or intraventricular hemorrhage, Chiari malformation due to myelomeningocele, encephalopathy, meningitis, and other CNS abnormalities. The causal factors of hydrocephalus and ventriculomegaly widely vary, from neuronal adhesion, vesicle trafficking, dystroglycanopathies, ciliopathies, RASopathies, planar cell polarity, and neural tube defects, lysosomal storage disorders, growth factors, Wnt signaling pathway, PI3K/AKT/mTOR pathway to transcription factors.

Due to recent advances in sequencing technologies, four genes have been well-known to cause congenital hydrocephalus; L1CAM\textsuperscript{125–129}, AP1S2 (X-linked), and CCDC88C MPDZ (autosomal recessive). Additionally, more than 100 genes were identified as the causal factors of genetic hydrocephalus or ventriculomegaly.\textsuperscript{121}

$L1CAM$ located at Xq28, mediates cell-cell adhesion, the guidance of neurite outgrowth, bundling, myelination, and pathfinding, long-term potentiation, neuronal cell survival, migration, and synaptogenesis. $L1CAM$ gene mutation results in invariable neurological phenotypes, such as hydrocephalus, AOCC or hypoplasia, and adducted thumbs (Fig. 17). Due to the X-linked recessive inheritance, the carrier mother’s male fetus has a 50% chance of being affected.

CSF flow pathway is also affected by abnormal beating or asynchronism of the ependymal cilia, which line the ventricular system. Therefore, ciliopathies such as Bardet-Biedl syndrome ($CEP290$\textsuperscript{130}), Meckel syndromes ($MKS1$, $TMEM67$\textsuperscript{131–133}), and Joubert syndromes ($TMEM216$, $CC2D2A$\textsuperscript{134}) are often connected with ventriculomegaly (Fig. 18).

Muscular dystrophies are associated with the aberrant glycosylation of α-dystroglycan and are collectively termed dystroglycanopathies.\textsuperscript{135} Dystroglycanopathies are often associated with brain and ocular pathology. Disorder of neuronal cell migration results in cortical maldevelopment and subsequent ventricular enlargement in cases of dystroglycanopathy. Walker-Warburg syndrome ($POMT1$, $PONT2$, and $B3GALNT2$), Muscle–eye–brain disease ($POMGnT1$), and Fukuyama congenital muscular dystrophy ($FKTN$) are representative dystroglycanopathies.\textsuperscript{135}

In several other overgrowth syndromes, PI3K/AKT/mTOR pathway-related genes are identified.\textsuperscript{136} The megalencephaly-capillary malformation-polymicrogyria syndromes (MCAP) and megalencephaly-polymicrogyria-polydactyly-hydrocephalus syndrome (MPPH) are classified in the spectrum of megalencephaly-associated syndromes.\textsuperscript{136} In megalencephaly-associated syndromes. The mechanism of ventriculomegaly is that megalencephaly induces polymicrogyria and cerebellar overgrowth, leading to oppression of the posterior fossa and cerebellar tonsillar herniation\textsuperscript{136}, which eventually obstructs CSF flow. However, since Chiari malformation doesn’t always exist, CSF flow obstruction may occur within the overgrown brain.\textsuperscript{137}
Mutations of growth factors related to genes (like FGFR3 can lead to skeletal dysplasia (Thanatophoric dysplasia) with enlarged ventricles associated with overgrown and hyper-convoluted posterior temporal lobe\textsuperscript{137} (Fig. 19).

When no other structural abnormalities have been notified prenatally, the term isolated ventriculomegaly is often used. However, in many cases of “isolated prenatally” ventriculomegaly, extra-CNS abnormalities or single-gene mutations may be found after birth. Chromosomal microarrays, exome sequencing, genome sequencing, and viral antibody analysis are recommended to elucidate causal genetic factors. In addition, a longitudinal observation is quite important because the spontaneous resolution of ventriculomegaly during pregnancy is occasionally seen in some of the mid-gestational isolated ventriculomegaly cases (Fig. 20).

\textit{In Utero Brain Injury and Damage}

In cases of neonatal encephalopathy and cerebral palsy, ‘is the timing of the causative event prenatal, intrapartum, or
ascertaining prenatal evidence of in utero brain damage that can cause postnatal neurological disorders is difficult. Reliable modalities for detecting prenatal brain injury are neurosonography and neuro MRI. However, in full-term infants with normal BPD without ventricular enlargement and a reassuring pattern observed on fetal heart rate monitoring at birth, brain damage is not suspected, and later on, brain damage from the fetal period may be suspected based on symptoms such as cerebral palsy. In such cases, brain damage postpartum? is a point to be discussed because it involves medical, social, legal, and ethical issues. Brain damage may be associated with prenatal events such as cerebral hemorrhage, encephalopathy, and migration disorder. It is not always possible to identify when the event occurred. In the case of monozygotic twins, the timing of the encephalopathy may be speculated, such as sIUFD (Fig. 21) or medical intervention for twin-to-twin transfusion syndrome or twin reversed arterial perfusion (TRAP) sequence (Fig. 22). However,
Secondary ventricular dilatation is often seen due to stenosis or occlusion of the foramen of Monro by thrombosis.

Primary intraventricular hemorrhage (IVH, Fig. 25) is defined when there are obvious intraventricular events such as choroid plexus tumor or bleeding. Primary IVH incidence is approximately 30%, and the rest 70% is secondary IVH. The most regular cause of secondary IVH is intraparenchymal hemorrhage in the periventricular area extending into the ventricular system, as shown in Figure 26. The IVH grading system in the infant was first reported by Papile et al. \(^{147}\) Grade I is isolated to the periventricular (subependymal) germinal matrix. Grade II implies 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.

**Conclusion**

As introduced in this chapter, fetal 3D neurosonography provides information on the orientation of the fetal brain, brain development during pregnancy, the exact location of brain lesions, and the inner structure of the lesions. In pediatric neurology, the relationship between cortical dysplasia and developmental abnormalities or intractable epilepsy is currently being discussed.\(^{132}\) In addition, molecular genetic techniques have revealed many genetic variants associated with brain morphological abnormalities that cause developmental delay, learning disabilities, epilepsy, and mental retardation, and the field of fetal neurology has been established.
Detailed neuroimaging is now available for diagnosis of the central nervous system, and genetic tests such as chromosomal microarrays, exome sequencing, and genome sequencing add information on genetic causative factors. The combination of detailed neurosonography and molecular genetics has established a new interdisciplinary field of fetal neurology called “neurosonogenetics,” which will enable accurate perinatal management and care in the future.

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