＜Special Issue: Toward a better understanding the pathomechanism of brain malformations＞

Fetal Neuroimaging of Neuronal Migration Disorder by Ultrasound

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Abstract: Imaging technologies have been remarkably improved and contributed to prenatal evaluation of fetal central nervous system (CNS) development and assessment of CNS abnormalities in utero. A new field of fetal neurology has been established by remarkable contribution of three dimensional/four dimensional (3D/4D) ultrasound technology. Most of congenital anomalies of the central nervous CNS have been demonstrated by prenatal ultrasound.

Neuronal migration, which occurs as early as the third month of gestation, is controlled by a complex assortment of chemical guides and signals. When these signals are absent or incorrect, neurons do not end up where they belong to. This migration disorder can result in structurally abnormal or missing areas of the brain in the cerebral hemispheres, cerebellum, brainstem, or hippocampus.

Clinically, prenatal diagnosis of migration disorder by antenatal ultrasound is quite difficult, and furthermore, the phenotype of migration disorder is apparent after eight month when gyration and sulcation are conspicuous. Earlier detection of migration disorder before gyration is one of challenges in a field of prenatal neuroimaging. Sylvian fissure changes its appearance between 20 and 30 weeks of gestation in normal fetuses. Therefore, to observe Sylvian fissure is the most comprehensive way for prenatal detection of migration disorder.

Key Words: Fetus, Prenatal, Ultrasound, Migration disorder.

Introduction

Imaging technologies have been remarkably improved and contributed to prenatal evaluation of fetal central nervous system (CNS) development and assessment of CNS abnormalities in utero. A new field of fetal neurology has been established by remarkable contribution of three dimensional/four dimensional (3D/4D) ultrasound technology[1-6]. Fetal neuroimaging by recent advanced technologies of sophisticated ultrasound and MRI has contributed to a field of fetal medicine, to detect prenatally many

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CNS congenital anomalies such as prosencephalic disorders, neurulation disorders, intracranial tumors, cysts, brain damage due to intrauterine insults and the prenatal assessment of fetal CNS has provided with proper prenatal/postnatal managements.

In the developing brain, neurons migrate from the areas where they are born to the areas where they will settle into their proper neural circuits. Neuronal migration, which occurs as early as the third month of gestation, is controlled by a complex assortment of chemical guides and signals. In the early second trimester, smooth brain surface without sulcation is observed. Neuronal migration occurs between three and five gestational months. As a consequence of migration, brain is matured with gyration and sulcation is observed after eight months (Fig. 1). When these signals are absent or incorrect, neurons do not end up where they should belong to. This migration disorder can result in structurally abnormal or missing areas of the brain in the cerebral hemispheres, cerebellum, brainstem, or hippocampus, including, resulting in schizencephaly, porencephaly, lissencephaly, agyria, macrogyria, pachygyria, microgyria, micropolygyria, neuronal heterotopias (including band heterotopia), agenesis of the corpus callosum, and agenesis of the cranial nerves.

Not a few brain malformations are closely related to neuronal migration disorders[7]. Clinically, however, prenatal diagnosis of migration disorder by antenatal ultrasound is quite difficult, and furthermore, the phenotype of migration disorder is apparent after eight months when gyration and sulcation become conspicuous. Earlier detection of migration disorder before gyration is one of challenges in a field of prenatal neuroimaging. In this article, normal and abnormal cortical appearances detected by prenatal ultrasound are described.

Normal cortical development

Neuronal migration occurs between three and five months. In early brain development, nerve cells

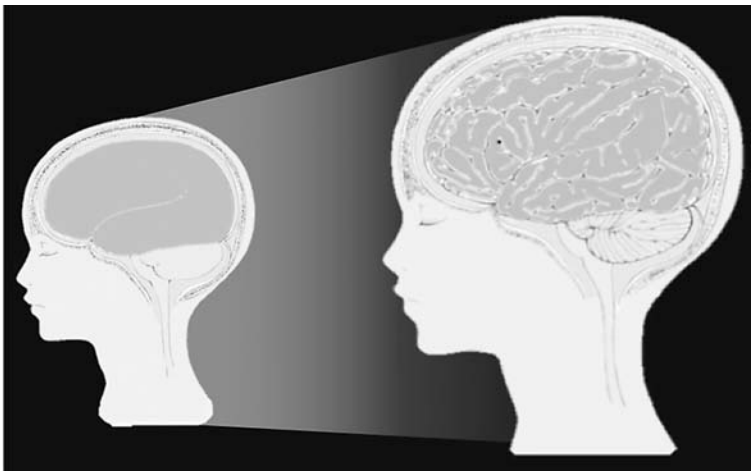

Fig. 1. Changing appearance of fetal brain during pregnancy
In the early second trimester (left), smooth brain surface without sulcation. Neuronal migration occurs between three and five gestational months. As a consequence of migration, brain is matured with gyration and sulcation (right) after eight months.

travel to their final destinations to populate and form the six layers of the cerebral cortex. When the brain first forms, neurons are generated in a region of ventricular zone and from there, they travel by crawling to reach the cortical surface. There are two modes of migration; tangential migration and radial migration[8)9)]. The first and earlier mechanism is movement by translocation of the cell body. This results in the preplate formation. The second mechanism is radial migration, in which migrating cells are generated by the radial glial progenitors. Travel instructions and guides on how to reach where they are going are served to migrating cells and these processes are controlled by a complicated molecular machinery.

As mentioned above, phenotype due to migration disorder on the surface of cerebral hemispheres appears in the late pregnancy, therefore it seems to be not possible to detect migration disorder before gyration. Toi and his colleagues[10)] reported normal sulcation pattern during pregnancy depicted by transabdominal ultrasound imaging. During pregnancy, the first evidence indicating the consequence of migration is the Sylvian fissure[11-13)] and the most comprehensive cutting section, in which bilateral Sylvian fissures are well demonstrated, as shown in Fig. 2. This cutting section is taken by sonogram via anterior fontanelle as an ultrasound window. During the latter half of the second trimester, the cortical structure macroscopically develops and the most distinct morphological difference appears to be the different structure of Sylvian fissure. Thus, the Sylvian fissure is one of the landmarks indicating

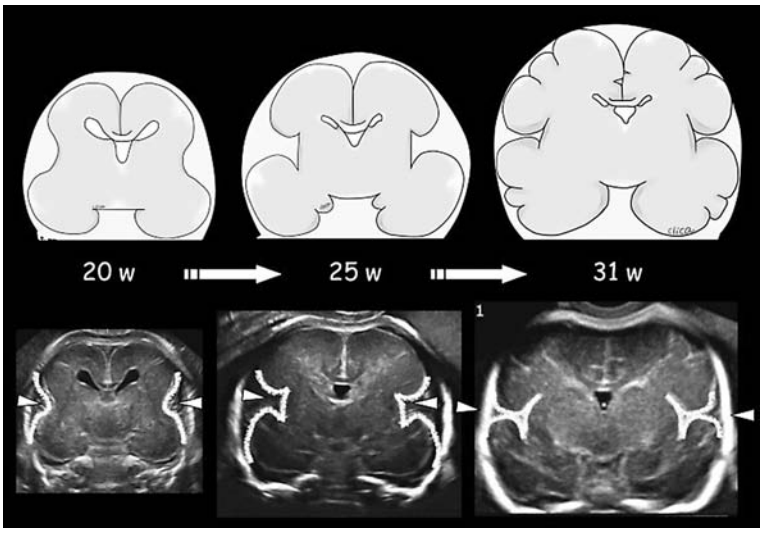

Fig. 2. Changing appearance of Sylvian fissure in the anterior coronal section by transvaginal sonography

At 20 weeks of gestation, bilateral Sylvian fissures (arrowheads) appear to be indentations (left). With cortical development, Sylvian fissures are formed with sharp edges during the latter half of second trimester (middle) and become as lateral sulci in late pregnancy. Sylvian fissure appearance is one of the most reliable ultrasound markers for the assessment of cortical development.

cortical development by normal migration.

Sonographic images of migration disorder before gyration

Developmental delay of the Sylvian fissures during the second and third trimesters may lead to suspicion of migration disorder. The author experienced two interesting cases. The first case was referred at 24 weeks and 5 days. The case was referred due to fetal small head. Bilateral parietal diameter was −3.4 SD and head circumference was −4.0 SD. In the coronal cutting section, the bilateral Sylvian fissures appeared to be definitely abnormal compared to normal development as shown in Fig 3. 6 q partial duplication and 6 q partial deletion were found by SNP microarray in this case. The second case was referred at 21 weeks of gestation due to fetal growth delayed. Micrognathia and low set ear were found but there is no other conspicuous abnormality. In the anterior coronal section of the brain at this stage, the development of bilateral Sylvian fissures appeared to be a bit delayed, compared to normal case (Fig. 4, left). However, this is not enough evidence to make a diagnosis of migration disorder therefore it was quite difficult to counsel parents. At 25 weeks of gestation (Fig. 4, right), the bilateral Sylvian fissures were definitely abnormal and thereafter the abnormal cortical development of pachygyria was demonstrated in late pregnancy.

Conclusion

Some of migration disorders have lead to very severe prognosis. Considering that migration disorder already occurs before fetal viability but that detection of brain lesions is mostly in the third trimester, early detection of migration disorder with severe prognosis will be one of our missions in fetal neuroimaging.

As described in this article, prenatal diagnosis of migration disorder is one of difficult fields missions in an antenatal diagnostic field. As the screening of cortical development and maldevelopment, observation of the Sylvian fissures in the anterior coronal cutting section may be recommendable.

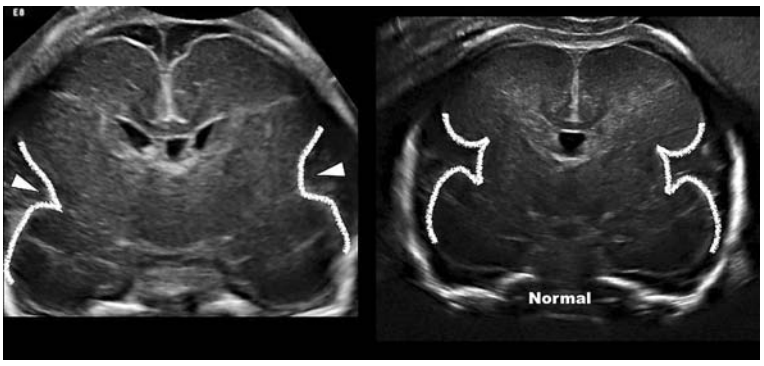

Fig. 3. A case of migration disorder at 25 weeks of gestation
(left) Ultrasound image of anterior coronal section. Abnormal Sylvian fissures (arrowheads) are demonstrated. Right image is the normal Sylvian fissures at the same gestational age.

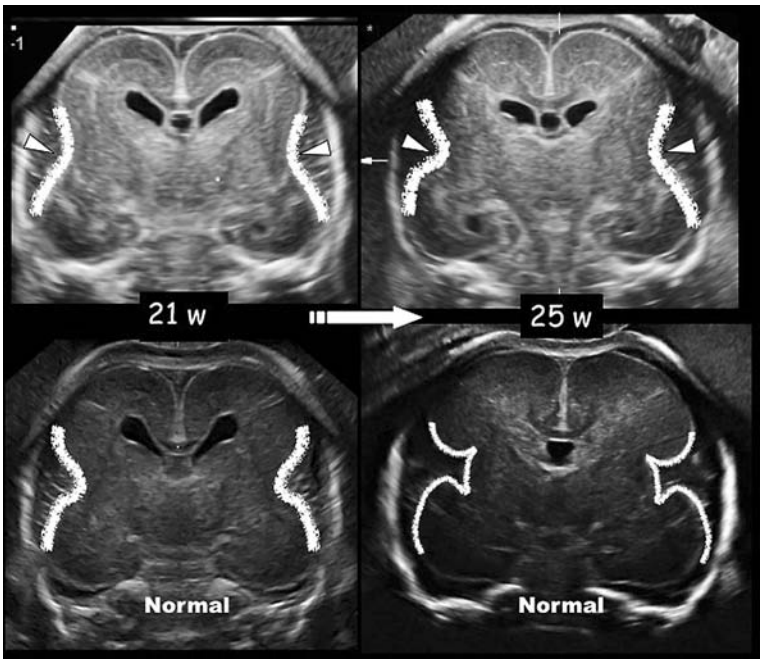

Fig. 4. A case of migration disorder at 21 and 25 weeks of gestation
(upper) Ultrasound images of anterior coronal section at 21 weeks (left) and 25 weeks (right) of gestation. At 21 weeks of gestation (upper left), the Sylvian fissures (arrowheads) appear to be abnormal compared with normal case (lower left) but it is not enough evidence for migration disorder. However, at 25 weeks of gestation (upper right), the development of Sylvian fissures (arrowheads) were definitely abnormal compared with normal case (lower right). Thereafter, abnormal cortical development of pachygyria was seen in late pregnancy.

However, this section is not always acquired by ultrasound during the screening scan of the fetal brain. Once we have the suspicion of migration disorder, MRI is the strong modality for demonstration of the cortical development, especially in the late pregnancy.

No conflict of interest in this article.

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〈和文抄録〉

胎児超音波による神経細胞移動障害の診断

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最近の超音波技術は飛躍的に向上し，胎児の中枢神経系（CNS）の発達や子宮内 CNS 異常の出生前評価に寄与してきた．胎児神経学という新分野が 3 次元／ 4 次元超音波技術のめざましい発展により確立され，CNS 先天奇形のほとんどは出生前超音波検査によって描出されるようになった．

妊娠 3 ヶ月から起こる神経細胞移動は細胞が増殖した後に限られた空間内において細胞を最終目的地に整然と配置する過程で神経細胞移動により機能分化した神経細胞は正しく信号を伝達する．この細胞移動の障害は，脳のあらゆる部位に表現型として出現しうる．

脳神経の細胞移動障害を胎児期に超音波検査で描出することは非常に難しく，さらに細胞移動障害の表現型は脳回脳溝形成が明らかとなってくる妊娠 8 ヶ月以降でないと明瞭にならない．脳回形成以前に細胞移動障害を早期発見することは，出生前の胎児神経画像診断の分野における課題である．シルビウス裂は正常な胎児で妊娠 20〜30 週の間に外観がめざましく変化するがこれが最初に顕著に表現される細胞移動の結果である．したがって，シルビウス裂を観察することで細胞移動障害の早期画像診断が可能となると考えられる．

キーワード：胎児，神経細胞移動障害，出生前，超音波検査．

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