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Application Status and Prospect of Craniocerebral Ultrasound in Neurodevelopment of Premature Infants

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Abstract: The purpose of this paper is to review the current status and future direction of the application of Cranial Ultrasonography (CUS) in the monitoring of brain development in preterm infants. A systematic search of the relevant literature and a comprehensive analysis of the data in these literatures indicate that CUS can provide real-time information about the structural and hemodynamic changes in the brain of preterm infants, which can help to identify neurodevelopmental abnormalities at an early stage, and that the application of new technologies, such as ultrasound elastography, ultrasound microfluidics, and ultrasonography, has further enhanced the assessment capability of CUS. Although the use of artificial intelligence algorithms such as deep learning in monitoring the neurodevelopment of preterm infants is still in its early stages, its promising future in clinical applications is of far-reaching significance. The monitoring of brain development of preterm infants by CUS is effective and accurate, providing more accurate brain development monitoring and more effective treatment programs for preterm infants.

Keywords: CUS; Preterm infants; Brain development; Neurodevelopment; Research progress

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1. Introduction

With the rapid development of perinatal medicine, the birth rate of preterm infants continues to rise worldwide [1]. However, preterm infants often face severe challenges of neurodevelopmental disorders due to their immature physiological development. Especially, as the core of the human body function, the development of the brain directly affects children's future cognitive, motor, and other neurological functions. Therefore, close monitoring of their brain development has become essential [2]. Early assessment of brain development in preterm infants is of great significance for the prevention and improvement of neurodevelopmental problems. Cranial Ultrasonography (CUS) plays an important role in the neonatal intensive care unit (NICU) because of its convenience, nonradiation, cost-effectiveness, and real-time dynamic monitoring [3]. CUS can capture the brain structure and hemodynamic changes of preterm infants in real time, providing clinicians with intuitive and powerful evaluation tools, which are helpful in formulating accurate treatment plans.

This review aims to comprehensively analyze the application status of craniocerebral ultrasound in monitoring brain development in preterm infants and explore the research progress of craniocerebral ultrasound in evaluating brain structure, monitoring cerebral blood flow, and predicting neurodevelopmental prognosis. Through in-depth analysis of the existing literature, this article aims to reveal how craniocerebral ultrasound can help clinicians better understand the complex process of brain development and its potential risks in preterm infants, and to look forward to the future development direction. With the continuous progress of new ultrasound technology, cranial ultrasound is expected to play a broader and deeper role in the monitoring of brain development in preterm infants.

2. Brain development before birth

The development and maturation of the brain is an intricate and long journey from the fetal period, the neonatal period, and the adult period [4]. The development of the nervous system begins in the ectoderm, where the neural tube grows and differentiates to give rise to the brain and spinal cord. At about the third week of embryonic development, the neural plate begins to form and is completely transformed into the neural tube during the following week, and its apical part continues to evolve into the brain. By the end of the fourth week of embryonic development, the tip of the neural tube develops into the forebrain, midbrain, and hindbrain. The forebrain develops most rapidly, and its front part gradually develops into two cerebral hemispheres, while the posterior part of the forebrain develops into the thalamus and hypothalamus. The development of the midbrain is relatively slow. The hindbrain and the endbrain evolved into the pons and cerebellum, respectively, and the medulla oblongata. In the middle of pregnancy, as nerve cells proliferate, differentiate, and migrate to various regions of the brain, the cerebral cortex begins to form, and gradually forms sulci and gyri. The hindbrain and the endbrain gradually form the pons, cerebellum, and medulla oblongata, while the cerebellum develops on the dorsal side of the brainstem and covers it. The inner lumen of the neural tube forms the main structure of the ventricle, and the shape of the ventricle is closely related to the development of the brain. The two lateral ventricles, the third ventricle, and the fourth ventricle, which evolved from the anterior cerebral bubble cavity, constitute the ventricular system. The lateral ventricle is connected to the third ventricle through the interventricular foramen, while the mesencephalic aqueduct connects the third and fourth ventricles.

In the development of the central nervous system, myelination begins in the fetal period. It is a process in which axons are encapsulated by lipid substances, which is closely related to the conduction of nerve impulses and cognitive function. White matter is mainly composed of axons, which are lighter in color and are responsible for the transmission of signals between the two cerebral hemispheres. Gray matter, which is darker in color and composed of neuronal bodies, dendrites, and glial cells, is mainly responsible for the processing of brain information, such as perception, movement, and cognition, which plays a key role.

3. Neurodevelopmental abnormalities in preterm infants and their influencing factors

Preterm infants are those born before 37 weeks of gestation. According to the World Health Organization definition, preterm infants are divided into several categories: extremely preterm (<28 weeks of gestation), very preterm (28–32 weeks of gestation), and moderate-to-late preterm (32–37 weeks of gestation). Preterm infants face many risks of poor health and neurodevelopmental outcomes due to their low gestational age. Neurodevelopmental immaturity in preterm infants is associated with poor vascular autoregulation, incomplete myelination of white matter, and incomplete proliferation and differentiation of cortical cells [5]. According to the principle of the "two-hit" hypothesis, G et al. demonstrated that the factors of abnormal brain development in preterm infants may be caused by a combination of developmental disruption and external injuries (including hypoxia, mechanical ventilation time, low glucose, etc.) [6]. If the whole process of neurodevelopment is disturbed at any stage, the neonatal neurodevelopment will be affected.

A common form of hypoxic brain injury in preterm infants is germinal matrix hemorrhage and intraventricular hemorrhage (GMH-IVH). Stem cells in the germinal matrix differentiate into neurons and then migrate to functional areas of the cerebral cortex, which typically dissipate by 35 weeks of gestation. The vascular network of the germinal matrix is the most blood-rich region of the developing brain. Especially in preterm infants with a gestational age of less than 32 weeks, their vascular system is not mature, and their ability to autonomously regulate blood flow is weak. Especially, fetal distress in utero or asphyxia during delivery, electrolyte imbalance, respiratory failure, and other conditions may lead to neonatal cerebral ischemia and hypoxia, and vascular rupture and hemorrhage [7–8]. In turn, it can cause complications such as post-hemorrhagic hydrocephalus and leukomalacia.

Another serious brain injury in preterm infants is white matter injury (WMI) [9]. White matter is mainly located in the arterial watershed region. During the third trimester of pregnancy, with the active development of paraventricular vessels and the maturation of oligodendrocytes, the white matter is particularly vulnerable to injury. Oligodendrocytes are responsible for forming the myelin sheath, a structure that is very sensitive to ischemia [10]. In addition, the role of gut microbes in the neurodevelopment of preterm infants has gradually become prominent, forming a microbiota-gut-brain axis, which affects the occurrence of WMI in preterm infants through metabolites produced by gut microbes, and also regulates cytokines and mediates oxidative stress [11]. The lack of microbiota and its metabolites may aggravate WMI in preterm infants. Preterm infants with white matter damage may present with a variety of neurodevelopmental abnormalities, including cognitive impairment, learning and memory impairment, impaired motor coordination, language impairment, audio-visual impairment, hyperactivity, emotional problems such as anxiety and depression, and even serious complications such as cerebral palsy [12, 14].

4. Application of cranial ultrasound in the assessment of brain development in preterm infants

4.1. Evaluation of brain development by two-dimensional ultrasound

Two-dimensional ultrasound is usually performed through the unclosed fontanelle of children, and a small convex or linear probe is selected for sector scanning. The fontanelle includes the anterior fontanel (commonly used), the lateral fontanel, and the mastoid fontanel, which are all transparent windows of cranial ultrasound examination. Craniocerebral ultrasound is a detailed assessment of brain development in children through specific ultrasound sections. Two-dimensional cranial ultrasound can be used to evaluate the development and maturation of the brain, which can be monitored as follows: identification of brain structures; Evaluation of the ventricular system; observation of sulci and gyri [14–15].

4.1.1. Identification of brain structures

The degree of brain development was evaluated by measuring the diameters of the main brain structures (transverse diameter of the brain, frontal lobe thickness, insula, length of corpus callosum, ventricular system, basal ganglia, brain stem, cerebellum, etc.). The diameter of brain structures in preterm infants is smaller than that in term infants, and the overall brain volume is smaller.

Sun et al. showed in their study on the correlation between neonatal cranial ultrasound indicators and neurodevelopment that there were differences in the length of the corpus callosum, the length of the cerebellar vermis, and the area and perimeter of the insula in neonates with neurodevelopmental abnormalities, and the brain diameter of neonates with neurodevelopmental abnormalities was smaller than that of neonates with normal development [16]. Liu et al. showed that the growth rate of the corpus callosum in some very low birth weight preterm infants with severe intellectual or motor development abnormalities was lower than that in the normal group at 3–6 weeks after birth, which was similar to the conclusion of Anderson et al. [17–18]. Many years ago, the decrease in the growth rate of the corpus callosum before 6 weeks after birth can serve as a warning factor for abnormal brain neurodevelopment in preterm infants. In a prospective study of very low birth weight preterm infants, Huang et al. evaluated the linear growth of the corpus callosum and the cerebellar vermis by cranial ultrasound [19]. After a corrected gestational age of 30.5 weeks, the growth rate of the corpus callosum was 1.72 mm/week, and the growth rate of the length of the cerebellar vermis was 0.78 mm/week. This may be helpful for early identification of preterm infants at risk of neurodysplasia and timely intervention. Zhou et al. conducted a study on the correlation between brain ultrasound manifestations and gestational age and birth weight in preterm infants at different gestational ages [20]. Gestational age was negatively correlated with the average gray value of white matter in the basal ganglia, frontal lobe, parietal lobe, and occipital lobe, while birth weight was also negatively correlated with the average gray value of the above brain tissue. The results indicate that the average gray value of brain tissue can be used to evaluate the development of the neonatal brain and provide important reference information for clinical practice.

4.1.2. Evaluation of the ventricular system

By observing the size and shape of the lateral ventricle, septum pellucidum, the third ventricle, and the fourth ventricle, the authors evaluated whether there was ventricular expansion or hydrocephalus, so as to explore its effect on the brain nerve development of premature infants. Ventriculomegaly (VM) refers to an increase in the volume of the ventricles caused by the accumulation of cerebrospinal fluid. Ventriculomegaly is the most common cause. Obvious ventriculomegaly is often accompanied by other structural abnormalities or chromosomal abnormalities, which are closely related to children’s intellectual and motor development [21]. The ventricular system of premature infants is not fully developed and does not retract. Ultrasound examination can observe that the shape of the ventricle is extended, S-shaped, or wider than that of the full-term infants, which may be related to the maturity of brain tissue and the characteristics of cerebrospinal fluid circulation.

4.1.3. Observation of sulci and gyri

The greater the gestational age at birth, the more gyri, the deeper the sulci, the more tortuosity, and the smaller the cerebral space. Two-dimensional ultrasound of the brain of premature infants can show that the brain parenchyma is fine, the cerebral sulci and gyrus are less, the cerebral sulci are shallow, and even the cerebral sulci structure is not formed, and the differentiation of the insula is not complete.

4.2. Assessment of brain development by 3D ultrasound

Three-dimensional ultrasound technology began to be used in pediatric brain examination in the 1980s, which can provide morphological imaging and quantitative volume analysis after multi-directional scanning of the brain. Compared with two-dimensional ultrasound, the images are richer and more three-dimensional, and the brain structure is more intuitive, and the judgment of brain volume is more accurate. Maria et al. measured the whole brain volume, thalamus, frontal cortex, and cerebellum volume of premature infants and newborns at different gestational ages at one month after birth using three-dimensional ultrasound, and compared the results with the neurodevelopment results of children at two years old [22]. The study found that the brain volume of children with neurodysplasia was significantly reduced, and had high accuracy. Isabel et al. used cranial ultrasound (US) to continuously measure the brain volume of preterm infants until corrected term, and established cross-sectional and longitudinal reference values of cerebellar size in preterm infants, suggesting that extrauterine life may affect the growth of the cerebellum, resulting in impaired cerebellar development [23]. Three-dimensional cranial ultrasound technology can also provide a comprehensive assessment of brain development in preterm infants, combined with other new ultrasound technologies. With the further development and application of technology, three-dimensional ultrasound is expected to provide a more accurate and comprehensive assessment method for the brain development of preterm infants.

4.3. Evaluation of brain development by ultrasound cerebral blood flow parameters

Transcranial Doppler ultrasound (TCD) is one of the non-invasive techniques for monitoring cerebral blood flow, which plays an important role in evaluating the brain development of premature infants. This technique accurately measures the blood flow velocity, resistance index, and other blood flow parameters of the main cerebral arteries (such as the middle cerebral artery (MCA) and anterior cerebral artery (ACA)). To explore the relationship between cerebral blood flow and brain development. Arditi et al. found that in extremely preterm infants, higher right MCA systolic velocity was associated with worse neonatal perception, and higher left MCA systolic velocity was associated with higher Mental Development Index (MDI) scores at 24 months, findings that suggest the impact of left-right cerebral blood flow differences on neurodevelopment [24]. CAI et al. investigated the association between hemodynamic parameters of the middle cerebral artery (MCA) and neurodevelopment in preterm infants [25]. The peak systolic velocity (PSV) and end diastolic velocity (EDV) of the neurodysplasia group were significantly lower than those of the good prognosis group, while the pulsatility index (PI), resistance index (RI), and the ratio of peak systolic velocity to end diastolic velocity (S/D) were significantly higher than those of the good prognosis group. The results of these studies suggest that clinicians, Early evaluation of cerebral blood flow in preterm infants is of great clinical significance for predicting later brain nerve development. In addition, in a recent study, Kenichi et al. studied the relationship between intracranial venous (ICV) pulsation and intraventricular hemorrhage (IVH), and found that severe IVH had persistent and significant intracranial venous pulsation, and pulsation index (ICVPI = minimum/maximum ICV velocity) may help to predict severe IVH [26]. This is of great significance for reducing the adverse brain consequences of preterm infants.

4.4. New ultrasound technologies

4.4.1. Elastography

Ultrasound elastography, including strain elastography (SE), transient elastography (TE), and shear wave elastography (SWE), uses ultrasound to apply pressure to tissues and calculate tissue deformation to evaluate tissue stiffness and infer tissue physical properties and composition through non-invasive mechanical action. Elastography can be used to quantitatively or semi-quantitatively evaluate the changes in brain tissue stiffness, which provides a new perspective for the diagnosis of brain development and lesions. Neuronal differentiation, glial cell proliferation, gyri formation, and myelination may affect brain stiffness. Therefore, the changes in stiffness between preterm and term infants can reflect the differences in developmental stages [27]. Albayrek and Kasap compared the brain stiffness of term and preterm infants using SWE and observed that the stiffness of various regions of the brain of term infants was higher than that of preterm infants, similar to Kim et al.'s study [28–29]. Wang et al. showed in their study that the mean elastic modulus values of periventricular white matter, thalamus, and choroid plexus in preterm infants were lower than those in term infants, and the BMI of preterm and term infants was positively correlated with the mean elastic modulus values of bilateral periventricular white matter, thalamus, and choroid plexus [30]. Therefore, ultrasound elastography is expected to become a new method for predicting delayed brain development or poor prognosis in preterm infants.

4.4.2. Superb microvascular imaging

Superb microvascular imaging (SMI) is an advanced non-invasive ultrasound Doppler technology, which can clearly display the low-velocity microvascular network in the brain, including the striatum and the extrastriate vessels [31]. With fetal development, the distribution, density, and flow velocity of the above vessels also change. SMI can monitor these changes in real time and provide quantitative indicators for brain maturity. Superb microvascular imaging technology is eager to provide a non-invasive and highly sensitive tool for the detection of brain maturity in neonates or premature infants, and has broad clinical application prospects. With the update and iteration of ultrasound instruments, it may become a major auxiliary tool for neonatal brain functional imaging in the future.

4.4.3. Contrast-enhanced ultrasound technology

Contrast-enhanced ultrasound (CEUS), also known as contrast-enhanced ultrasound (CEUS), improves the visualization of blood vessels by injecting a microbubble contrast agent into the body, allowing more accurate qualitative and quantitative assessment of brain perfusion [29]. In the field of neonatal brain imaging, CEUS technology can provide a more accurate delineation of brain microblood flow than traditional ultrasound technology. In 2013, Kastler's group showed that contrast-enhanced ultrasound through the anterior fontanel (TCEUS) was more accurate than magnetic resonance imaging (MRI) in the diagnosis of neonatal brain lesions [32]. As an emerging diagnostic technology, CEUS is being more and more widely used in the diagnosis of central nervous system diseases in children. Ceus not only enriches the diagnostic methods of traditional ultrasound, computed tomography (CT), or MRI, but also is more suitable for children due to its high safety [33]. With its unique imaging ability, CEUS technology has shown great potential and application prospects in the diagnosis of neonatal brain diseases, and provides a powerful diagnostic tool for pediatricians.

5. Challenges and future directions of cranial ultrasound in brain development

Since the 1970s, computer technology has helped medical diagnosis, especially medical image analysis. In 2006, deep learning, especially convolutional neural network (CNN), made a major breakthrough in image recognition. At present, deep learning is mainly used to analyze MRI to monitor the brain development of premature infants

[34–35]. However, due to the limitations of ultrasound images, such as dynamic scanning and low resolution, the related research of deep learning is in its infancy [36]. However, ultrasound images are non-invasive and real-time monitoring, which has the potential to monitor the brain development of preterm infants. CNN has been used in MRI analysis, but its application in ultrasound images is still in its infancy. Researchers hope to overcome the technical difficulties, improve the processing accuracy and reliability, and promote the use of computer language to make a major breakthrough in the assessment of brain development in preterm infants.

Future research will focus on the development and optimization of deep learning algorithms, aiming to improve the quality of ultrasound images and enhance the recognition of brain development features in preterm infants. Using advanced image processing technology to reduce noise and enhance key brain structures, and exploring the fusion of MRI and USI data to accurately assess brain maturity and developmental changes. Multi-modality imaging fusion will facilitate the discovery of comprehensive biomarkers and the early identification of developmental deviations. The self-adaptability and learning ability of deep learning algorithms will optimize ultrasound image analysis and improve the accuracy of brain structure segmentation. With the continuous progress of ultrasound and computer technology, personalized precision medical programs will provide stronger support for the monitoring of brain development in preterm infants.

6. Conclusions

This article reviews the application status, current problems, and future development of CUS in monitoring brain development in preterm infants, and highlights the absolute advantages of ultrasound in the NICU. By elaborating the evaluation methods of brain structure, ventricular system, and cerebral sulci and gyrus, it is proved that craniocerebral ultrasound provides strong support for the early identification of neurodevelopmental abnormalities in preterm infants. In addition, with the introduction of ultrasound cerebral blood flow parameters and new technologies such as elastography, superb microvascular imaging, and contrast-enhanced ultrasound technology, the application of cranial ultrasound in the evaluation of brain development in preterm infants is more promising. In the future, with the continuous progress of technology, craniocerebral ultrasound is expected to play a more accurate and comprehensive role in the monitoring of brain development in preterm infants, provide more detailed and reliable diagnostic information for clinical practice, help optimize treatment plans, and improve the prognosis of cerebral neurodevelopment in preterm infants.

Disclosure statement

The authors declare no conflict of interest.

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