REVIEW ARTICLE

Brain Assessment from Fetus to Neonate in Terms of Morphology and Function: Role of Neonatologist

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Abstract

Assessment of the structure and function of the brain was enabled by the development of ultrasound (US) technology, which may depict how complicated developmental processes of the brain structure in utero can result in complex behavior of embryo and fetus. Extrauterine life is the continuation of intrauterine life, and transposing our knowledge of brain structure and function from prenatal to postnatal life is an important approach to making the distinction between normal and abnormal brain development and the early diagnosis of various structural or functional brain abnormalities. The invention of four-dimensional US (4D US) enabled the introduction of the Kurjak Antenatal Neurodevelopmental Test (KANET), which opened up a new field of fetal neurology. The KANET is a standardized and comprehensive method to evaluate fetal neurological condition objectively and reproducibly by observation of fetal behavior and general movements (GMs). Based on the existing investigation, if the KANET score is normal, then there is a high probability that the development of the infant will be normal, with a very low probability that the child with developmental delay would have been missed, while the prediction is more complicated if the score is abnormal or borderline.

Keywords: Brain, Four-dimensional, Fetal behavior, Function, Neonate, Structure, Ultrasound.

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Introduction

It was in 1895 when Wilhelm Conrad Röntgen invented X-rays, which has been considered the turning point in the diagnosis of many diseases.[1] Although this ingenious invention improved many fields of medicine, the human brain remained inaccessible till the development of the computed axial tomography scan by Godfrey Hounsfield some 80 years after Röntgen's discovery.[2] The development of embryology, physiology, and sophisticated imaging, electrophysiological, genetic, and other neurological diagnostic procedures enabled better insight into the developing human brain.[3] Assessment of the structure and function of the brain was enabled by the development of US technology, which may depict how complicated developmental processes of the brain structure *in utero* can result in complex behavior of embryo and fetus.[4–10] Extrauterine life is the continuation of the intrauterine life, and transposing our knowledge of brain structure and function from prenatal to postnatal life is an important approach to making the distinction between normal and abnormal brain development and the early diagnosis of various structural or functional brain abnormalities.[4–13]

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The brain is a very dynamically developing organ with long-lasting developmental processes till the beginning of the 70s of human life, which make the study of this organ very complicated and challenging.[14,15] In an infant born at term, characteristic cellular layers can be observed in motor, somatosensor, and visual and auditory cortical areas.[15–17] While proliferation and migration are completed in a term infant, synaptogenesis, neuronal differentiation, and myelination continue very intensively.[15] Impairment of the brain is very high due to very complicated development, which is making brain congenital anomalies among the most prevalent.[15] As dynamics of the developmental changes of the brain is highest in pregnancy, most of the brain injuries occur in utero, while intrapartal and postnatal disorders are much less frequent.[15] It is questionable whether there is a possibility to diagnose structural and/or functional disorders of the brain in utero to predict the clinical picture of the disease after birth. With the development of fetal neurology using 4D US, it has become possible to assess fetal behavior as a promising screening tool to detect those fetuses at high risk for the development of neurodevelopmental disorders.[18] As the development of the brain is a unique and continuing process throughout gestation, and after birth, it is expected that there is also a continuity of fetal and neonatal movements, which are an indicator of the developmental processes of the brain.[18]

The aim of the paper is to present how changing brain structure influences behavior from fetal to neonatal life.

Impaired Brain Function and Neurological Disability

The structurally or functionally abnormal fetal or neonatal brain may result in neurological disability either pre or postnatally.[19–21] Most neurologically impaired infants belong to low-risk pregnancies, as epidemiological studies showed.[22–25] Cerebral palsy (CP), as the most prevalent neurologic disability of movement and posture, has several clinical presentations, among which dyskinetic CP is the dominant type of CP in term-born, appropriate-for-gestational-age children with severe neurological impairments, who have frequently experienced adverse perinatal events.[22–25] In comparison with typically developing children, individuals with CP have much more issues related to decreased quality of life throughout their lifespan.[23] Diagnosis of CP is made for a lifetime, and detecting individuals who are at increased risk either pre or postnatally may be advisable to avoid developmental catastrophe, which may become evident later in life.[23] Sometimes, CP relates to heredity, which may increase the risk for its development by 4.8 times if there is one child diagnosed with CP, while with twins, this risk is 29-fold.[26–28] Some genetic research found genetically mediated dysregulation of early neuronal connectivity in CP, with some 14% of cases attributed to an excess of damaging de novo or recessive variants.[27]

Cerebral palsy (CP) is the most common childhood physical disability, with the prevalence in high-income countries of 1.4–2.5/1,000 live births and 2–4/1,000 live births in low-income countries in the entire pediatric population, while in very immature infants, it could be 70–100 times higher.[29] Although the etiology of CP is quite unclear, it mostly appears due to acquired or congenital brain developmental disorders.[29] CP is the disorder of posture and movement resulting in less prevalent dyskinesia (4%), ataxia (1%), and hypotonia (2%) affecting all four limbs, or most prevalent spasticity (92%) which may be unilateral (hemiplegia in 59%) or bilateral (including diplegia with mostly affecting lower extremities), and tetraplegia and quadriplegia affecting all four limbs and the trunk.[29] There are also mixed types of CP which are rare.[29] With decreasing chronological age, the brain plasticity of children is increasing, giving the window of opportunity for evidence-based early intervention, which may result in better functional outcomes with fewer complications.[29]

Most commonly, CP is diagnosed during the second or the first year of life and only in severe cases before the age of 6 months.[30] If the symptoms of CP are mild, sometimes it is not easy to make the diagnosis of CP before the age of several years.[30] According to the American Academy of Pediatrics, all children should be screened for developmental delay at regular well-baby check-ups at the age of 9, 18, 24, or 30 months, depending on the severity of symptoms.[30] Most of the even mild symptoms of developmental delay can be found till the age of 30 months.[30] If the screening tests at mentioned chronological age give the reason for concern, the doctor will refer the child for medical and developmental evaluations and early intervention.[30] If the child has a high risk of developing CP, the early intervention should start as soon as possible, that is, at a critical developmental time for the plasticity of the developing brain.[29]

Fetal and Neonatal Neurology: Are They Related?

Postnatal assessment of the brain begins with the history and clinical assessment, usually followed by neuroimaging and neurophysiological assessment to find out the possible etiology and pathophysiology of impairment. The most frequently used neuroimaging methods are cranial US, magnetic resonance imaging (MRI), magnetic resonance spectroscopy, and diffusion weighted imaging in very low birth-weight premature infants and in term infants with encephalopathy regardless of the etiology.[31–35] Diagnosis of CP is not easy despite consensus definition and suggestions the ways to reduce diagnostic variability in the diagnosis of CP, especially in scenarios featuring genetic etiologies or hypotonia as the cause of nonprogressive motor disability in which only 46–67% of practitioners would diagnose CP.[36] On the other hand, most of the child neurologists (76%) thought that they should be involved in the diagnosis of CP, although only 42% of their patients have been diagnosed with CP by child neurologists, while 18% did not receive the referrals to

establish the diagnosis of CP.[37] This was the reason to search the ways how to increase the probability of an early diagnosis of CP, which would enable timely early intervention with a possibly better outcome.[34] Standardized assessment tool, including assessment of writhing GMs, and Hammersmith Neonatal Neurological Examination together with fidgety GMs, and Hammersmith Infant Neurological Examination (HINE) has been proposed as the clinical tools for the early postnatal prediction and diagnosis of CP.[34]

Although neurological assessment of the neonate is important, it is not reliable for early diagnosis of CP.[38] There are several methods used for the clinical assessment of infants from the neonatal period onwards. Neurological assessment at term by Amiel-Tison (ATNAT) is based on neurological maturation assessing the lower subcortical system developing earlier from the reticular formation, vestibular nuclei and tectum, and upper cortical system developing from the corticospinal pathways.[39,40] The role of the lower system is to maintain posture against gravity, while the upper system is responsible for the control of erect posture and for the movements of the extremities.[39,40] At the corrected age (CA) of 40 gestational weeks, optimality assessment consists of head circumference measurement, assessment of cranial sutures, visual pursuit, social interaction, sucking reflex, raise-to-sit and reverse, the passive tone in the axis, the passive tone in the limbs, fingers, and thumbs outside the fist, and autonomic control during the assessment.[39,40] The ATNAT is increasing accuracy in assessing central nervous system function in the neonate by using a simple scoring system, focusing on the most meaningful items, promoting a clinical synthesis at term, for term and preterm infants.[39,40] ATNAT at 40 weeks had a positive predictive value of 33% and a negative predictive value of 88%, respectively, with similar results for neurodevelopmental assessment at the age of 3 months.[41] ATNAT has been used in everyday clinical practice from the neonatal period till the age of 6 years, but recently more used and published method of clinical quantitative and qualitative assessment is the HINE which is a validated scored assessment of 26 items, each scored from 0 to 3, used to evaluate infants between 2 and 24-months' CA.[42] A global cut-off score of <57 out of a maximum of 78 at 3 months' CA is widely accepted as predictive of CP at 3–4 months' CA with high sensitivity (90–96%) and specificity (85–87%).[42,43]

As described by Prechtl, GMs are spontaneous movements appearing at 7.5 GW prenatally till the age of 60 postmenstrual weeks postnatally.[44–46] They begin postnatally as preterm GMs, then with the maturation of the brain continuing as the writhing and finishing as fidgety GMs appearing at certain postnatal age as smooth and unpredictable movements, showing variability in the intensity, range, direction, and complexity.[47] The preterm and writhing GMs are not predictable for CP, while the fidgety movements appearing at 52–54 weeks of postmenstrual age are classified as normal, abnormal, sporadic, or absent.[47] If absent fidgety GMs are strongly correlated with abnormal neurodevelopmental outcomes.[47] In many systematic reviews, abnormal fidgety GMs are considered a reliable predictor of CP.[48,49]

Currently, a combination of GMs, the HINE, and neonatal MRI is the gold standard for the diagnosis of CP in high-risk infants and can be used to accurately predict CP before 5 months' CA.[43,48]

Signs of Postnatal Neurological Assessment Used Prenatally

Kurjak et al. by using 4D US and introducing the KANET was at that time convinced that 4D US compared to two-dimensional (2D) US, opened up a new field of fetal neurology by the introduction of a standardized and comprehensive method to evaluate the fetal neurological condition objectively and reproducibly by observation of fetal behavior and GMs.[50,51] However, from the postnatal neurological assessment, one can learn that making a neurological diagnosis based only on the assessment of motoric function or even the evaluation of GMs is almost impossible because much more should be learned from neuroimaging and electrophysiological and other diagnostic means.[52,53] By postnatal clinical neurologic assessment, clinicians are evaluating many more components like cognitive function, cranial nerves, motor strength, sensation, reflexes, coordination, gait, emotion, learning, self-control, and memory[52,53]. It is not possible to add all these components to prenatal assessment using only 4D US. Although the KANET has added some components from prenatal neurological assessment proposed by Amiel Tison in ATNAT like cranial sutures, high arched palate, and neurological thumb, which before the introduction of KANET have not been used in prenatal 2D US neurological evaluation based mostly on the assessment of GMs.[54,55]

From the investigation of Kurjak and ass, it has been pointed out that if the KANET score is normal, then there is a high probability that the development of the infant will be normal, with a very low probability that the child with developmental delay would have been missed.[52,53] If the KANET score is abnormal in a high-risk fetus with a positive family history of CP, there is a high probability that postnatal development may appear abnormal.[52,53] However, if the KANET score is borderline even in high-risk pregnancy, postnatal development of the child may appear either normal, borderline, or abnormal.[52,53] Possibility of a high false-positive rate in those fetuses with borderline KANET would indicate postnatal prospective neurodevelopmental follow-up.[52,56,57] Early diagnosis of CP in high-risk infants can be made before the CA of 5 months by using the following predictive tools—term-age MRI (86–89% sensitivity), the Prechtl Qualitative Assessment of GMs (98% sensitivity), and the HINE (90% sensitivity) with the proposed algorithm proposed by Novak et al.[57] For the low-risk infants with abnormal KANET scores the protocol should be individualized and follow-up established on

a case-by-case basis.[52] The future development of fetal neurology should be multidisciplinary with special emphasis on scrutinized postnatal follow-up of infants who had abnormal and borderline KANET scores and were born from high-risk pregnancies.[52] The KANET assessment is a very time-consuming procedure, which is considered a screening method to discriminate between normal and abnormal fetal behavior. There has been an investigation on the use of artificial intelligence in the assessment of GMs postnatally, which should be investigated for the prenatal assessment of fetuses by 4D US to decrease the costs and workload of medical professionals.[58]

Conclusion

Even with 4D US, it is not easy to perform the neurological assessment of the fetus by combining some postnatal signs and an assessment of the quality of GMs. By using a prenatal assessment tool named KANET for neurodevelopmental assessment of the fetus, we are still hardly ready to predict postnatal neurodevelopment even in two extreme situations for fetuses assessed as abnormal or optimal, while for those who are in utero in a gray zone (so-called borderline), the prediction of postnatal development is even more complex.[52]

Based on the existing investigation, if the KANET score is normal, then there is a high probability that the development of the infant will be normal, with a very low probability that the child with developmental delay would have been missed.[52] However, if the KANET score is borderline and especially if abnormal in high-risk pregnancy, the postnatal development of the child may appear abnormal.[52] Due to a high false-positive rate in those fetuses, thorough postnatal prospective neurodevelopmental follow-up, especially in high-risk infants with a positive family history of CP, should be advised. For low-risk infants with abnormal KANET scores, the postnatal diagnostic protocol should be individualized, and follow-up should be established on a case-by-case basis.[52] Postnatal multidisciplinary approach is advisable with a special accent on detailed postnatal follow-up of infants from high-risk pregnancies who were scored as abnormal and borderline on KANET assessment.[52]

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