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Continuity between fetal and neonatal neurobehavior

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SUMMARY

The human brain is very sensitive to environmental changes affecting its growth and development. Environmental changes influence neonatal behavior after birth, enabling continuity between prenatal and postnatal behavior, but postnatal adaptation could be considered as discontinuity. Thus there is the question of environmental discontinuity between intrauterine conditions characterized by existence of microgravity and extrauterine life with gravity as a developmental condition sine qua non. Four-dimensional ultrasound is currently being assessed as a functional prenatal screening test for detection of neurological impairment in utero. The Kurjak Antenatal Neurodevelopmental Test (KANET) combines the assessment of fetal behavior, general movements, and three out of four signs that have been postnatally considered as symptoms of possible neurodevelopmental impairment (neurological thumb, overlapping sutures and small head circumference). Although the KANET has been tested on normal and high-risk pregnancies, the significance of the test for detection and prevention of neurodevelopmental disability is still questionable.

1. Introduction

The development of ultrasound and other imaging techniques has enabled better insight into the gravid uterus and its content, nevertheless many aspects of the intrauterine environment remain unexplored.[1] Though quite different from the postnatal environment, but intrauterine conditions are required for normal development of all organs and their systems.[2] Environmental changes influence neonatal behavior after birth, enabling continuity between pre- and postnatal behavior, but postnatal adaptation could be considered as a discontinuity. Thus there is the question of environmental discontinuity between intrauterine conditions characterized by existence of microgravity and extrauterine life with gravity as a developmental condition sine qua non.[2,3]

The human brain is very sensitive to environmental changes affecting its growth and development.[4] The brain of very tiny prematurely born babies is unable to follow the genetically programmed growth pattern even when postnatal feeding and nurturing of the babies is conducted.[4] As part of an attempt to discover a correlation between impaired structure of the central nervous system and its functional impairment, four-dimensional (4D) ultrasound has been assessed as a functional prenatal screening test for detection of neurological impairment in utero.

The aim of this chapter is to examine the continuity of brain function from pre- to postnatal life with special consideration of the environmental changes occurring after birth.

2. Development and the growth of the brain

It is estimated that the mature human brain has 86 billion neurons in total and 85 billion non-neuronal cells.[5] Cerebral cortex represents 82% of the brain mass with 16 billion neurons, i.e. 19% of total brain neurons.[5] Among primates, humans possess the largest number of neurons from which to derive cognition and behavior as a whole.[5] Neocortex, in evolutionary terms a new and rapidly evolving brain structure in mammals, has a similar layered architecture across species over a wide range of brain sizes.[6] Larger brains require longer fibers to communicate between distant cortical areas; the volume of white matter that contains long axons increases disproportionally faster than the volume of the gray matter that contains cell bodies, dendrites, and axons for local information processing.[6]

Development of the human brain remains incomplete at the end of pregnancy and even for decades afterwards.[7–9] The processes of brain development such synaptogenesis, neuronal differentiation and myelination continue for many years after birth, while characteristic cellular layers are present in motor, somatosensory, visual

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and auditory cortical areas in the brain of term infants.[7–9] The complicated nature of these developmental processes renders the brain liable to impairment, including the possible development of congenital malformations. Brain tissue is very sensitive to any kind of pre- or postnatal injury, which may result in developmental disorder or brain damage.[7] Most injuries occur during pregnancy and labor, whereas postnatal brain damage is not so frequent.[7] Therefore it is reasonable to make an effort to diagnose fetuses with brain damage – a challenging task prompting the development of fetal neurology. As brain development is a unique and continuing process throughout gestation and after birth, it seems reasonable to expect continuity of fetal and neonatal behavior that can serve as a functional indicator of these developmental processes.[3,7–9]

With respect to growth, the pre- and postnatal potential in humans varies, with a tendency to slow down after birth.[10] It seems as though the potential for growth differs pre- and postnatally, and this issue remains controversial.[10] There is long-standing evidence that postnatal growth restriction in extremely low birth weight infants affects brain growth, resulting in decreased head circumference and more developmental disabilities years after birth.[11,12] It is also evident that development of brain volume is affected inversely, and the surface of the brain is even more affected from birth to the age of 12 years in children who have experienced white matter damage in infancy.[12,13] This could be explained by nutritional stress at critical times during development having persistent and potentially irreversible effects on organ function.[14] Cortical growth is achieved predominantly by an increase in surface area rather than in thickness, and during late development of the human fetus a rapid increase in brain size occurs with considerable development of cortical surface area relative to cerebral volume, manifested in the development of cortical convolutions.[15] It may be speculated that development of morphology and function should be in equilibrium during different developmental stages in order to avoid developmental disability.

3. Cerebral palsy and related developmental disorders

There is still uncertainty concerning the appearance of neurological disability originating from the fact that some severely brain-damaged children are functionally completely normal and vice versa. On the other hand there is awareness of many factors which may be protective for the developing brain. The data on brain damage originate from epidemiological studies. Brain damage is dependent on the gestational age at the time of birth. Extremely preterm babies have about 100-fold increased prevalence of cerebral palsy (CP) compared with term-born infants.[16] Prevalence of CP is also birth weight dependent.[17] There is evidence that the prevalence of CP is higher in term infants born at 37, 38, 39, 41 and 42 gestational weeks compared with those born at 40 weeks.[18] Increased prevalence of dyskinetic CP in term infants has been observed in recent decades, which is of great concern.[19] Genetic factors are also involved in the etiology of CP, which impedes understanding.[20] It is unknown why the frequencies of etiologic factors for CP are different for term and preterm infants; it is estimated that in term infants prenatal factors account for 38%, peri/neonatal factors for 35% and postnatal factors for 21%, whereas for premature infants the same factors are present in 17%, 49% and 33%, respectively.[21] Whether by ignorance or convenience, and despite substantial epidemiologic evidence demonstrating that peripartum hypoxia cause no more than 10% of all cases of CP, intrapartum mismanagement and resultant hypoxic–ischemic encephalopathy remain uppermost in the minds of non-obstetric care providers as the major causes of CP.[22]

CP and related developmental disorders are more frequent in males than in females, but the reasons for this disparity are uncertain.[23] Males born very preterm also appear to be more vulnerable to white matter injury and to intraventricular hemorrhage than females.[23] Experimental studies in adult animals and data from adult patients with stroke indicate that sex hormones such as estrogens provide protection against hypoxic–ischemic injury, and the neonatal brain is also influenced by these hormones.[23] Other reports demonstrated major differences between male and female neurons grown separately in cell culture, suggesting that sex differences in the fetal or neonatal period result from intrinsic differences in cell death pathways.[24] This information indicates that there are important neurobiological differences between males and females with respect to their response to brain injuries.

Although there is a possibility of intervening in cases of brain damage using neuroprotective therapy, its efficacy is still questionable in newborn infants except for the whole body or only head cooling in term infants, whereas application of the same treatment in premature infants is still controversial.[25–27]

After discharge there is the possibility of early intervention, which may lead to some improvement in neurodevelopmental outcome.[28]

These data indicate that earlier diagnosis of potential risk or neurological impairment result in better outcome. This was the main reason why there was an attempt to introduce a simple and universally applicable neurological test for fetuses, hoping that the time will come when prenatal intervention in some fetuses with a pathological test would become possible.[29]

4. Is there evidence for fetal neurological disability?

Cerebral palsy is a postnatal neurological disability with precise definition, although it is still not clear at what postnatal age the diagnosis should ultimately be made, because there have been cases with cessation of motor symptoms in more than 51.5% of 7-year-olds who were previously diagnosed with CP.[30–32] Normalization of motor signs was observed more frequently in black than in white children.[31] However, 13% of white children and 25% of black children whose motor signs resolved were mentally retarded (IQ <70) at 7 years of age.[31] Non-febrile seizures, abnormalities in speech articulation and extraocular movements, and certain abnormalities of behavior were more frequent among children who 'outgrew' cerebral palsy than in the general population of the study.[31] This was the reason why in some studies the age 4 years has been set for the definite diagnosis of CP when recheck of the previously affected patient has been recommended.[30] On the other hand, the definition of CP as 'a group of permanent disorders of the development of movement and posture, causing activity limitation, that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain' stimulates medical professionals to search for 'non-progressive disturbances' of fetal and infant brain.[33] It is well documented that inflammation is one of the most important etiologic factors pre- and postnatally.[34,35] There is evidence from rat brains that the profile of neuroinflammatory responses presented striking variations according to age: no or down-regulated anti-inflammatory responses associated mainly with interleukin-1β (IL-1β) release in preterm-like rat brains, by contrast with term-like rat brains presenting stronger anti- and pro-inflammatory responses, including both IL-1β and tumor necrosis factor-α releases, and blood–brain barrier leakage.[34] These developmentally dependent variations of neuroinflammatory response could contribute to the differential pattern of brain lesions observed across gestational ages in humans with the necessity to