Cognitive Evolution in the Perinatal Period

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Abstract

Neurological development is a complex process in which the nervous system reaches its fullness in adulthood stage. This development begins before birth, continues in both the last months of gestation and in the first months after birth, in response to a continuous remodeling due to the ability of nerve cells to eliminate excess components through apoptosis. One of the most important and ambitious objectives of developmental neurology is the early identification of those at risk for the development of subsequent disabilities: an early rehabilitation intervention can improve the quality of their life. The most important long-term outcome of periventricular leukomalacia is represented by spastic diplegia, which is also the most frequent motor deficit associated with prematurity. This high incidence seems to be due to the specific localization of the lesion involving the cortico-medullary bundles descending from the motor areas assigned to the movement of the lower limbs. In the presence of larger lesions, which also involve the semi-oval center, tetraparesis can be found accompanied by severe alteration of the intellectual function. The follow-up of the high-risk child and newborn is now established in the most developed countries. Physiotherapy is a relatively recent therapeutic modality in the Intensive Care Units and is performed through different techniques, with the aim of reducing respiratory work, maintaining airway viability and improving ventilation and gas exchange, improving neurosensory skills. A sensitive period for performing an intervention with a set schedule is from birth to 24 months of correct age. The program is tailored to the child and his family. An intervention program must promote the neurobehavioral development of the child, the quality of the organization and of the relational, sensorial, motor and cognitive skills and their integration, with the aim of an adequate development, without the pretension of modifying or accelerating its natural learning.

1. Introduction

Over the past two decades, advances in perinatal care have helped to reduce mortality and severe neurological morbidity for extremely and very preterm neonates (Ancel et. al., 2015). However, motor and cognitive disabilities associated with mild-to-moderate white and gray matter injury are frequently present in this population (Marret et. al., 2013). The most common abnormality observed in contemporary cohorts is the diffuse component of white matter injury, evidenced by magnetic resonance imaging (MRI): about 50% to 80% of extremely and very preterm neonates have diffuse white matter abnormalities (WMA) which correspond to the minimum grade of severity (Back, 2014; Gano et. al., 2015).

Nevertheless, mild-to-moderate diffuse WMA has also been associated with significant deficits in motor and cognitive functions. The increased neonatal survival and the characteristics of diffuse WMA have increased the need to study the brain of the premature infant using non-invasive neuroimaging techniques sensitive to microscopic and/or diffuse lesions (Rutherford et. al., 2010). This is evident from the combination of intense pre-clinical and clinicopathologic research with neonatal neurology and quantitative neuroimaging research (Volpe et. al., 2011).

In the following article, we review literature relating the most frequent neuropathological patterns and recent neuroimaging findings in preterm newborns and infants with perinatal brain injury. Specifically, we focus on the use of neuroimaging and clinical neurological observation to aid diagnosis, and track long-term neurodevelopmental outcomes.

2. Neurological Development

Neurological development is a complex process in which the nervous system reaches its fullness in adulthood stage. This development begins before birth, continues in both the last months of gestation and in the first months after birth, in response to a continuous remodeling due to the ability of nerve cells to eliminate excess components through apoptosis.

According to David Barker's hypothesis, events that occur in a critical temporal window of the perinatal period permanently alter the trajectory of the subsequent development, determining permanent effects on the phenotype. This window of vulnerability corresponds to the brain at the third trimester of gestation, a period in which most neurons and synapses are formed and in which the cerebral cortex develops. According to Barker, the mother's womb is more important than the house. The premature birth abruptly interrupts the passage of biological messages between mother and fetus, therefore the fetus adapts to survive in a different environment. This adaptability is called plasticity and is the result of the interaction between the genes and the environment. The preterm's brain is a great example of plasticity: the greater the prematurity, the greater is its elasticity in adapting to events that deviate its normal path (Fanos, 2015). In the newborn with cerebral hemorrhage or asphyxiated damage, the neuronal cells close to the damaged ones are activated and take over the functions of the latter, due to a continuous remodeling process. This process has important consequences on the clinical features, as the resulting neurological dysfunctions are expressed by non-specific clinical signs. Neurological development follows a complex sequence of closely connected acquisitions: gross and fine motor skills, language and communication, cognitive function, affectivity and emotions, social behavior, personal autonomy. These sectors have a harmonious development, but with an extreme intrinsic variability that makes it even more difficult to recognize the para-physiological conditions.

3. Major Aetiological Factors of Perinatal Damage

In recent decades there has been a noticeable increase in the survival rate of extremely preterm infants, and for a while an increase in subjects with motor and sensory neurological handicaps has been feared. However, this increase is limited to the first years after the opening of the Neonatal Intensive Care Units, thanks to the use of cortisone in pregnant women at risk of premature birth, the centralization of pregnancies at risk, and the use of surfactant. The most recent studies indicate a decrease in neurological morbidity and the reduction of preterm subjects affected by PCI and/or severe sensorineural handicap. It is believed today that only 10-12% of premature infants present a severe neurological disability in school age (Sellier et. Al., 2015). This category of preterm infants, however, is at high risk of milder neurological problems: 25-50% have developmental problems that are less disabling but not negligible, because they afflict their and their family's life (scholastic difficulties and adaptation between peers) (Johnson & Marlow, 2016). These problems are called "more subtle neurological problems" and include motor delay, persistent neuromotor abnormalities, intellectual retardation, language problems, attention and hyperactivity disorders, disturbances in socialization and learning (Hutchinson et. Al., 2013).

One of the most important and ambitious objectives of developmental neurology is the early identification of those at risk for the development of subsequent disabilities: an early rehabilitation intervention can improve the quality of their life. The most common brain lesions in the premature infant are hemorrhage of the germinal and intraventricular matrix (GMH, IVH), post-hemorrhagic hydrocephalus, periventricular leukomalacia (PLV) in the cystic form and in the non-cystic form, also described as White Matter Abnormalities (WMA) or neuroaxonal disease in preterm encephalopathy.

WMA is the most common brain damage of the preterm at the end of the correct age, detected with MRI. It is often associated with ventricular dilatation, increased extracerebral spaces and reduced white matter (Volpe, 1999; Straticiuc et. al., 2016). The most important long-term outcome of periventricular leukomalacia is represented by spastic diplegia, which is also the most frequent motor deficit associated with prematurity. This high incidence seems to be due to the specific localization of the lesion involving the cortico-medullary bundles descending from the motor areas assigned to the movement of the lower limbs. In the presence of larger lesions, which also involve the semi-oval center, tetraparesis can be found accompanied by severe alteration of the intellectual function.

The long-term neurological sequelae of hemorrhage are related to two pathogenic moments; the first is represented by the hemorrhage itself and by its complications (Bolisetty et. al., 2013). In infants with periventricular parenchymal damage following a venous infarction, an evolution towards hemiplegia is almost constantly observed. Such symptom manifests itself only around 12 months of life, that is when the newborn, growing, begins to make use of the brain areas that have been damaged. The second pathogenetic moment underlying the neurological consequences of PVH / IVH is the destruction of neurons which, at the time of the insult, are in the germinative matrix, but which should have migrated to the cerebral cortex, between the second and the fifth layers (Payne, 2013). This event may explain some cognitive deficits and attentional disorders that are found in 25-50% of premature infants. Some studies have compared the brain conformation of premature infants with the brain of children of the same age, born at the end of pregnancy with the aid of MRI (Vasileiadis, 2004). In prematurely born children, more pronounced in those who had an episode of PVH / IVH, some brain regions were smaller than in the control group. More precisely, some areas of the motor cortex, premotor, temporal and parieto-occipital cortex have been shown to be reduced in volume. The cerebellum, the nuclei of the base, the amygdala, the hippocampus and the corpus callosum were significantly smaller too. On the other hand, a significantly larger volume was found at the level of the temporal and occipital horns of the lateral ventricles. These volumetric changes could be another cause of the neurological sequelae of preterm infants, especially those with PVH / IVH (Ferrari, 2017).

Finally, the cerebellar lesions are currently recognized as an important complication in newborns with severe prematurity: direct and indirect lesional mechanisms that alter brain growth have been called into question, damaging their neuro development. The cerebellum has always been considered a structure involved in fine and complex motor organization. In the last twenty years its important function of processing all the higher psychic functions has been clarified, such as language, visual and spatial abilities, memory, attention, social and affective behaviors, probably through modulatory effects on the cerebral cortex of frontal and parietal areas (Limperopoulos et. al., 2012).

4. Early Diagnosis and Intervention

Neuroimaging

It is possible to obtain brain images in the early neonatal period to aid the physician in determining the time and evolution of the injury. Cerebral ultrasonography is the most used diagnostic investigation in neonatology, being easily executable and repeatable at the patient's bed, although it remains an operator-dependent examination and with less sensitivity and specificity than MRI (Parodi et. Al., 2013).

Brain MRI is the most accurate diagnostic investigation for the assessment of the newborn's brain, but it has several critical aspects: it is an expensive investigation, it is not practicable at the patient's bed, it requires specific neuroradiological skills and the sedation of the newborn (Benders et. al., 2015). Neuroradiological investigations must be associated with clinical evaluations of the functional repertoire of the child before establishing a possible physiotherapy program (Ibrahim et. al., 2018; Ferriero, 2018).

Neurological Evaluation

Neurological evaluation includes: traditional neurological examination based on the search for evoked responses and the observation of spontaneous motility of General Movements. There are various tools to perform a standardized neurological evaluation with the aim of identifying neurological signs and their evolution, to determine the adequacy of brain development, to identify the presence of a disorder and to estimate a prognosis. The Infant Neurological Examination (HINE), developed at Hammersmith Hospital in London by Dubowitz, is a simple method, lasting 15 minutes, suitable for serious evaluations of the development of term and preterm infants (Maitre et. al., 2016; Romeo et. al., 2015).

In the late 1980s, Prechtl standardized and validated the General Movements Assessment (GMs) as a reliable tool for assessing spontaneous infant motility and as an excellent indicator of dysfunction and early brain damage. The fetal nervous system generates these patterns of movement that is a reflection of the spontaneous activity of the brain, result of complex neural networks, the central pattern generators, which are found in the brain, in the upper part of the medulla and in the brainstem. The GMs involve the whole body in a variable sequence of movements of the trunk, neck, legs and arms; their speed, strength and intensity increase and decrease, their beginning and end are gradual. The rotation along the axis of the limbs and the continuous changes in direction of movement make the GMs fluid and elegant and create the sensation of complexity and variability. If the nervous system suffers damage, the GMs lose their characteristics of complexity, variability and fluidity. The evaluation of GMs has a high predictive value, based on the gestalt perception of an appropriately trained operator (Guzzetta et. al., 2009; Guzzetta et. al., 2003; Einspieler et. al., 2016). The GMs of the preterm period are similar to those of the fetus, at the end they have a reduced width, showing a writhing character that gradually disappears when the fidgety character begins to emerge from the sixth week post-term. GMs are recognizable around the ninth and last until the twentieth week post-term (Ferrari et. al., 2016).

5. Conclusions

Brain damage in the perinatal period is the most common cause of preterm morbidity, and its identification and extension can be assessed by neuroradiological investigations.

Preterm infants are at risk of developing major (PCI) and minor degree of disabilities. PCI cannot be diagnosed before 2-3 years of age; the preterms that will develop a PCI have important anomalies of the posture and of the spontaneous movement at the first evaluations of the neurological examination. The traditional neurological examination (HINE), together with the evaluation of GMs, are valid tools to estimate early neurological and functional deficits related to brain damage (Novak et. al., 2017).

The association of serious neuroimaging and repeated neurological evaluations allow in most cases the early identification of children at risk of neuromotor disability including PCI (Lupu et. al., 2017).

The follow-up of the high-risk child and newborn is now established in the most developed countries. Physiotherapy is a relatively recent therapeutic modality in the Intensive Care Units and is performed through different techniques, with the aim of reducing respiratory work, maintaining airway viability and improving ventilation and gas exchange, improving neurosensory skills. A sensitive period for performing an intervention with a set schedule is from birth to 24 months of correct age. The program is tailored to the child and his family. An intervention program must promote the neurobehavioral development of the child, the quality of the organization and of the relational, sensorial, motor and cognitive skills and their integration, with the aim of an adequate development, without the pretension of modifying or accelerating its natural learning.

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