Newborn & Infant Nursing Reviews 16 (2016) 8–12

Contents lists available at ScienceDirect

Newborn & Infant Nursing Reviews

journal homepage: www.nainr.com

Articles

Brain Injury in Preterm Infants: Pathogenesis and Nursing Implications

Susan Blackburn, RN, PhD, FAAN

Department of Family and Child Nursing, University of Washington School of Nursing, Seattle, Washington

ARTICLE INFO

Keywords:
Periventricular leukomalacia
Germinal matrix hemorrhage/intraventricular hemorrhage
Cerebellar hemorrhage
Preterm infant
Brain injury

ABSTRACT

Preterm infants are at higher risk for neurological alterations, with this risk increasing with decreasing gestational age due to both developmental and destructive elements. This article provides an overview of brain development and vulnerabilities in the preterm infant and examines the pathogenesis of three areas of brain injury seen in preterm infants: periventricular leukomalacia, germinal matrix hemorrhage/intraventricular hemorrhage, and cerebellar injury). Implications for nursing care of infants at risk for these disorders are discussed.

Preterm infants as a group are at higher risk for neurologic alterations. This is seen across all gestational ages, with the greatest prevalence in very low birthweight (VLBW) infants (infants <32 weeks gestation and 1500 g birthweight).[1,2] VLBW infants are at increased risk for cognitive, behavioral, attentional, and socialization problems along with motor deficits such as cerebral palsy. The most prominent long term alterations are cognitive deficits unaccompanied by motor deficits.[1,2] The prevalence of major disabilities (cognitive, motor, vision, hearing) increases with decreasing birth weight and gestational age and are seen in 6% to 8% of infants from 1501 to 2000 g, increasing to 14% to 17% at 1001 to 1500 g and 20%–30% in infants weighing <1000 g.[3] The higher prevalence of cognitive dysfunction (alterations in learning, memory, language, vision, hearing, attention and socialization, motor issues, and behavioral issues) continues into school age and adulthood (15% to 25% in those born at <1500 g and over 50% in those <750 g).[3,4]

Volpe notes that brain injury in preterm infants is a combination of developmental and destructive elements and "the importance of viewing clinical and anatomic consequences in the context of brain development."[5p.168] Preterm infants are more vulnerable to brain injury and altered brain maturation because "preterm birth occurs at a time of peak brain growth, synaptogenesis, developmental regulation of specific receptor populations, and central nervous system organization and differentiation."[6p.1157]

Sannia et al. discussed particular areas of brain vulnerability at different gestational ages and their consequences in terms of disorders that are most prominent at each age (although these disorders certainly can occur at any gestation).[5] For example from 23 to 26 weeks gestational age there is rapid development in the cerebellum and periventricular areas (both of which have germinal matrixes) with risks of germinal matrix hemorrhage (GMH)/intraventricular hemorrhage (IVH) and cerebellar hemorrhage (CH) most prominent , although these infants are also at risk for later periventricular leukomalacia (PVL). From 26 to 34 weeks gestational age white matter development is more prominent, especially in the periventricular zone as is PVH; GMH/IVH is less common after 30 to 32 weeks. From 34 to 36 weeks gestation, cortical volume increases (half of the cortical volume is achieved in the last 6 weeks of gestation) and myelinated white matter increases from 35 to 40 weeks. Later preterm infants most commonly have injury from circulatory impairment (stoke) or asphyxia. In term infants the most common disorders are perinatal stroke and hypoxic–ischemic injury.[5]

The focus of this article is to provide an overview of brain development and vulnerabilities in the preterm infant and examine the pathogenesis of three types of brain injury seen in preterm infants: PVL, GMH/IVH, and cerebellar injury. Finally, implications for nursing care of infants at risk for these disorders will be discussed.

Brain Development

Brain development in the embryo and fetus is characterized by six stages. The first two stages, neurulation (3 to 4 weeks) and prosencephalic development or ventral induction (5 to 6 weeks) set up the basic structure and major components of the brain. Neurulation involves development of the neural tube and neural plate, and closure of the neural tube (generally between 22 and 28 days).[6] Failure of the neural tube to close leads to neural tube defects (NTDs) such as anencephaly, spina bifida and encephalocele.[6,7] Periconceptional folic acid supplementation significantly reduces risk of NTDs.[8] Prosencephalic development leads to formation of forebrain, midbrain and hindbrain structures as well as the brain ventricles. Development of the face is associated with this stage so alterations in brain development are often accompanied by alterations in facial development.[6]

The third stage, neuronal proliferation, is characterized by formation of neurons (most prominent from 8 to 16 weeks), and later glial cells, in the subependymal germinal matrix. The germinal matrix contains neuronal and glial cell precursors.[9] This germinal matrix will remain prominent into the third trimester and is the usual site where GMH/IVH

Department of Family and Child Nursing, Box 357262, University of Washington, Seattle, WA, 98195-6272. Tel.: +1 206 543 8218.
E-mail address: sblackbn@UW.EDU.

http://dx.doi.org/10.1053/j.nainr.2015.12.004
1527-3369/

arises in preterm infants. The germinal matrix thickness begins to decrease after 24 weeks gestation and has almost disappeared by 36 to 37 weeks.[9] Neuronal proliferation is followed by migration (stage 4) of initially neurons and later glial cells from the germinal matrix to their eventual loci with the cerebrum.[1,10] Neuronal migration in the cerebral cortex is generally complete by about 5 month's gestation; neuronal migration in the cerebellum (which contains its own germinal matrix) continues into the postnatal period.[11,12] Glial cell migration continues into the eighth month.

The fifth stage of brain development is organization, which begins at 5 months gestation, is most prominent from then until the first 1–2 years postbirth, and continues into adulthood. During organization the central nervous system begins to develop the capacity to act as an integrated whole and for different areas of the brain to communicate with each other and other areas of the body.[13] This stage involves development of the neocortex (especially from 22 to 36 weeks gestation).[13] Major organizational processes include development of axons and dendrites to link nerve cells (neuron differentiation and arborization), development of synapses or points of communication within cells (synaptogenesis), balancing of excitatory and inhibitory synapses, glial differentiation and removing excess elements (neurons, synapses, connections) and refining synapses.[1,7,13] Preterm infants in the neonatal intensive care unit are in this stage of brain development. The final stage of brain development is myelination which lasts from around 8 month's gestation until early adulthood.[1,14]

Cerebellar Development

The cerebellum derives from the rhombencephalon (hindbrain). The cerebellar plate (seen by 12 weeks) includes neuroepithelial, mantle and marginal cellular layers. The neuroepithelium forms the external granular layer, which migrates inward to form the internal granular layer of the cerebellum which is comprised of neurons.[15] The external granular layer is a proliferative zone that gives rise to the various cell types of the cerebellum.[16] Most cerebellar neurons are granular cells and numbers of neurons in the cerebellum exceed numbers in the cerebral cortex.[15,16] Neuronogenesis in the cerebellar germinal matrix occurs between 3 and 4 months gestation, with migration from 3 to 8 months.[7,14] Cerebellar development accelerates from 20 to 30 weeks with peak thickness of external granule layer seen at 25 weeks.[15] Cerebellar development relies on the reciprocal interactions of excitatory and inhibitory/regulatory cell types that are rapidly developing in the third trimester. Between 30 and 40 weeks development continues at a rapid rate with a greater than 30-fold increase in surface area during this time.[13,15]

Glial Cells

Glia are supporting cells within the central nervous system (CNS) and continue to divide after birth. There are three types of glia: (1) myelin-building glia consisting of oligodendrocytes (in CNS) and Schwann cells (peripheral nervous system); (2) clean-up glia (astroglia, microglia) that remove waste, especially when neurons die and fill up vacated space; and (3) guiding glia such as radial glia in the CNS which guide the migrating neurons from the germinal matrix to their eventual loci within the cerebral cortex (these become astrocytes after brain maturation and Schwann cells that guide regenerating axon to target after peripheral damage).[1,6,13,17] Astrocytes, oligodendrocytes and microglia are particularly vulnerable in the preterm infant. Astrocytes undergo rapid proliferation from 24 to 32 weeks (peak 26 weeks) and are found primarily in deep cortical layers and white matter.[13] These glia assist with axonal guidance, growth, brain structural development, and functioning of blood–brain barrier, that can release transmitters (such as glutamate) to send signals to neighboring neurons and interact with neurons and synapses to help integrate information.[1,13] Oligodendrocytes during their premyelinating period prior to term, and especially prior to 32 weeks gestation, are especially vulnerable to hypoxic–ischemic injury and thought to play a role in the pathogenesis of periventricular leukomalacia.[18] Microglia are brain immune cells and macrophages and also have a role in brain development.[19] Peak numbers are seen in the third trimester. If activated due to cell damage such as occurs with hypoxia–ischemia or inflection/inflammation, the microglia release free radicals, cytokines and glutamate which can lead to further cellular injury.[1,5,13]

Pathogenesis of Brain Injury in Preterm Infants

Brain injury in preterm infants is characterized by multiple lesions including PVL, often with concomitant neuronal/axonal abnormalities, GMH/IVH that may be accompanied by posthemorrhagic infarction, cerebellar injury, and posthemorrhagic hydrocephalus.[1] Pathogenesis of these disorders involves both developmental and destructive elements. Knowledge of pathogenesis has increased in recent years, but questions still remain.

White Matter Injury (Periventricular Leukomalacia)

The most common type of brain injury seen in VLBW infants is PVL occurring in up to 50% of VLBW infants.[2] Infants are most vulnerable between 23 and 32 weeks.[4] The primary lesion in PVL is injury to the cerebral white matter, but PVL often occurs in conjunction with neuronal/axonal injury.[2,19] Disruption of glial and neuronal maturation may lead to later alterations in multiple areas of cerebral development and later neurodevelopmental problems across multiple domains.[4,20]

Two main types of PVL have been described: focal and diffuse. Focal injury is further subdivided into macroscopic injury, which evolves into cysts (cystic necrosis) and microscopic injury which evolves to glial scars (microscopic necrosis). Focal lesion involves degeneration of axons and glia in the injured area.[4,21] Microscopic injuries are more common than cystic injuries (which tend to be more severe).[1,4] Diffuse PVL is characterized by damage to pre-myelinating oligodendrocytes (pre-OLs) leading to hypomyelination, astrocystosis and microgliosis.[4,11,12] Diffuse white matter injury involves primarily astrocytes, microglia and degeneration of pre-OLs and leads to failure of myelination.[4] In recent years, studies have reported a shift from the more destructive cystic lesions to less severe chronic injury from the diffuse form (which are still associated with decreased cerebral growth and altered neurodevelopmental outcomes).[4] Back noted that this change to less severe injury is likely "related to changes in the timing, severity, and progression of H–I [hypoxic–ischemic] insults."[4p.3] Diffuse white matter injury involves primarily astrocytes, microglia and degeneration of pre-OLs and leads to failure of myelination.[4,18]

The interaction of three, maturation-dependent factors is thought to increase vulnerability of VLBW infants to PVL. These factors are (1) an immature vascular supply to the white matter so oxygen delivery is reduced; (2) immature cerebral autoregulation, and (3) the vulnerabilities of pre-OLs, which are rapidly differentiating and the major form of oligodendrocytes in VLBW infants.[1,2,5,19] The pathogenesis of cerebral white matter injury in preterm infants involves hypoxia and/or ischemia and infection and/or inflammation.[1,2,5,19,22] These events result in the release of extracellular glutamate (leading to excitotoxicity), reactive oxygen and nitrogen species, i.e. free radicals, (leading to oxidative stress) and proinflammatory cytokines (leading to inflammation).[22] As a result of these events, the vulnerable pre-OLs are damaged, microglia are activated, astrogliosis and scar formation occur, and neuronal/axonal damage with damage to both the white mater and gray matter may occur secondary to the original pathologic event.[22] Unfortunately, damage to the pre-OL leads to further release of these toxic substances. Vulnerability decreases as pre-OLs mature and differentiate into oligodendrocytes.[4]

PVL injury often occurs in conjunction with neuronal/axonal alterations primarily in the gray matter. Volpe termed the combination of PVL and concomitant neuronal/axonal injuries the "encephalopathy of