Neurobiology of Disease 92 (2016) 90–101

Contents lists available at ScienceDirect

Neurobiology of Disease

journal homepage: www.elsevier.com/locate/ynbdi

Review

Controversies in preterm brain injury

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ARTICLE INFO

Article history:
Received 15 July 2015
Revised 8 October 2015
Accepted 14 October 2015
Available online 23 October 2015

Keywords:
Preterm brain injury
White matter injury
Neuroimaging
Brain development

ABSTRACT

In this review, we highlight critical unresolved questions in the etiology and mechanisms causing preterm brain injury. Involvement of neurons, glia, endogenous factors and exogenous exposures is considered. The structural and functional correlates of interrupted development and injury in the premature brain are under active investigation, with the hope that the cellular and molecular mechanisms underlying developmental abnormalities in the human preterm brain can be understood, prevented or repaired.

Contents

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Available online on ScienceDirect (www.sciencedirect.com).

http://dx.doi.org/10.1016/j.nbd.2015.10.012
0969-9961/

1. The challenges of defining human preterm brain injury

Preterm infants are at high risk of brain injury and their injuries have been studied for many decades, but there are many unresolved questions regarding the etiology of this injury. Current debate in the field revolves around the relative contribution of impaired or delayed maturation versus specific injury, a debate reviewed here by focusing on: the contribution of specific cell types in gray and white matter; how these gray and white matter alterations change neuronal connections and circuit function; and the role of altered environment or injury in these changes.

There are several major reasons why human preterm brain injury is not a single well-defined entity. First, the clinical management of preterm infants varies widely leading to striking variability in neurological outcome even within a given geographic region (Bodeau-Livinec et al., 2008). Additionally, most neuropathology or neuroimaging studies are based upon subjects derived from tertiary/complex care hospitals that typically treat the most critically ill neonates who are at much higher risk for worse outcomes, thus skewing the data. By contrast, studies based upon subjects drawn from community-based hospitals may reflect a broader spectrum of outcomes that is more representative of the population. Second, preterm brain injury may be triggered or exacerbated by multiple factors that may be harmful for the preterm brain. These include hypoxemia, hypoxia–ischemia, maternal fetal infection, postnatal sepsis, inflammation, drug and toxicant exposures, pain, neonatal stress and malnutrition (Back and Miller, 2014). Third, pathophysiological triggers may be modified by additional factors unique to each preterm baby. These individual factors reflect the confluence of effects exerted by gender, genetics, epigenetics, socio-economic status, the integrity of the family unit and a whole host of other maternal–fetal factors (e.g., maternal smoking, drug or alcohol abuse) that influence the in utero environment and which may have triggered preterm birth. Fourth, there are significant technical challenges to study the human preterm brain. Access to human autopsy brains is very limited and the value of the tissue may vary widely depending on postmortem interval and the modes of tissue preservation (e.g., fresh, frozen, formalin fixed or paraformaldehyde fixed), limiting the application of many modern histological or molecular biology techniques. In contrast to pathology studies, neuroimaging studies can enroll large numbers of subjects, which allows for greater population sampling but may not detect certain types of early or small lesions that are beyond the current resolution of clinical MRI scanners (Back and Miller, 2014).

Compared to human studies, experimental animal approaches are invariably reductionistic and typically focus on a single insult (e.g., hypoxia–ischemia, chronic hypoxia, infection, inflammation or drug exposure), although there may be significant cross-talk between insults (e.g. inflammation resulting in hypotension and hypoxia). Most experimental studies rely upon rodents, because of the access to transgenic approaches, the greater feasibility of achieving replicates and the greater access to molecular reagents. However, there are substantial concerns with rodent studies that include significant developmental differences from human at the levels of brain anatomy, physiology, response to pharmacologic agents and triggers of injury, more accelerated postnatal brain maturation and fundamental differences in the biology of the major neural cell types (Back et al., 2012). Large preclinical animal models (e.g., fetal rabbit, sheep and non-human primate) offer some distinct advantages, but are costly, challenging to undertake, lack transgenic approaches and also retain some developmental differences from human. Thus, the question of whether a single factor causes the patterns of injury seen in preterm brain or whether a convergence of events is necessary has not yet been answered, but has profound implications for potential therapeutic strategies.

Table 1
Major areas under investigation in preterm brain injury: How do they combine to cause impairments?

Areas of investigation	Impairment type	Examples
Gray matter	Dysmaturation	Neuronal loss, reduced aborization, impaired neurogenesis
White matter	Dysmaturation	Arrest of oligodendrocyte maturation, glial loss
Axons	Dysmaturation	Loss of myelinated or unmyelinated axons, impaired conduction
Subplate neurons	Dysmaturation/injury	Loss leading to impaired thalamic-cortical connectivity
Endogenous growth factors, hormones	Dysmaturation/repair	Altered steroid or thyroid hormone exposure, recovery via endogenous growth factors
Inflammation, infection	Injury	Microglial activation altering glial and neuronal maturation, cell loss
Hypoxia–ischemia	Injury	Arrest of glial and neuronal maturation, cell loss
Iatrogenic factors	Injury	Exposure to steroids, narcotics, pain, abnormal sensory input altering development

2. Developmental delay versus injury

Preterm brain injury occurs during a phase of rapid brain development outside of the normal in utero environment leading to a combination of delays in normal maturation plus specific injuries associated with acute or chronic insults. Developmental delays after premature birth may arise from two major causes. First, a broad range of injuries can cause significant disruption to ongoing endogenous developmental events in the brain – either before or after delivery – thereby affecting fetal and/or postnatal developmental programs and their normal physiological timing. Second, abnormal exposure to specific factors or chemical compounds (e.g. inflammation, external stimuli, drugs) can cause abnormalities in developmental trajectories. These two main causes of developmental delays can occur concomitantly or in sequence, further worsening neurological outcome. The relative contribution of these two mechanisms—delay of normal maturation and injury—remains a major area of debate and investigation in the field.

The contribution of each of these changes is discussed here (see Table 1 for summary), highlighting critical unresolved questions. Factors that may alter preterm brain development are also discussed to highlight the injurious potential of endogenous and exogenous