Please cite this article in press as: Elitt CM, Rosenberg PA. The challenge of understanding cerebral white matter injury in the premature infant. Neuroscience (2014), http://dx.doi.org/10.1016/j.neuroscience.2014.04.038

Neuroscience xxx (2014) xxx–xxx

REVIEW

THE CHALLENGE OF UNDERSTANDING CEREBRAL WHITE MATTER INJURY IN THE PREMATURE INFANT

C. M. ELITT AND P. A. ROSENBERG *

Department of Neurology and the F.M. Kirby Neurobiology Center, Boston Children's Hospital, Boston, MA 02115, United States

Program in Neuroscience, Harvard Medical School, Boston, MA 02115, United States

Abstract—White matter injury in the premature infant leads to motor and more commonly behavioral and cognitive problems that are a tremendous burden to society. While there has been much progress in understanding unique vulnerabilities of developing oligodendrocytes over the past 30 years, there remain no proven therapies for the premature infant beyond supportive care. The lack of translational progress may be partially explained by the challenge of developing relevant animal models when the etiology remains unclear, as is the case in this disorder. There has been an emphasis on hypoxia–ischemia and infection/inflammation as upstream etiologies, but less consideration of other contributory factors. This review highlights the evolution of white matter pathology in the premature infant, discusses the prevailing proposed etiologies, critically analyzes a sampling of common animal models and provides detailed support for our hypothesis that nutritional and hormonal deprivation may be additional factors playing critical and overlooked roles in white matter pathology in the premature infant.

This article is part of a Special Issue entitled: Stress, Emotional Behavior and the Endocannabinoid System.

Key words: white matter, prematurity, oligodendrocyte, cerebral palsy, glutamate, nutrition.

Contents

INTRODUCTION

White matter injury (WMI) in the premature infant leads to substantial long-term motor and cognitive disabilities and remains one of the most challenging clinical problems in neonatal neurology. Very-low-birth-weight infants (< 1500 g) are particularly at risk, as 10–15% are diagnosed with permanent motor deficits (cerebral palsy) and 25–50% have significant cognitive, attentional, behavioral or socialization problems (Hack et al., 2005; Volpe, 2009; Mercier et al., 2010; Anderson et al., 2011; Anderson, 2013). The emotional and economic burdens of these deficits are large, with cerebral palsy costs estimated at nearly a million dollars per patient (Honeycutt et al., 2004). Since preterm birth rates are increasing in nearly all countries (Goldenberg et al., 2008; Blencowe et al., 2012), particularly in the very-low-birth-weight population at highest risk for WMI (Batton et al., 2011), the vulnerable cohort of infants will only grow. Somewhat surprisingly, the rate of preterm births in the United States more closely resembles that

*Correspondence to: P. A. Rosenberg, Department of Neurology, Boston Children's Hospital, CLS 13073, Boston, MA 02115, United States. Tel: +1-617-919-2634; fax: +1-617-919-2380.
E-mail address: paul.rosenberg@childrens.harvard.edu (P. A. Rosenberg).

Abbreviations: DHA, docosahexaenoic acid; E1, estrone; E2, estradiol; E3, estriol; EPA, eicosapentaenoic acid; GST, galactocereboside sulfotransferase; IGF-1, insulin-like growth factor-I; MBP, myelin basic protein; MOG, myelin oligodendrocyte glycoprotein; PLP, proteolipid protein; PLP1, proteolipid protein gene 1; pre-OL, premyelinating oligodendrocyte; PVL, periventricular leukomalacia; T3, triiodothyronine; T4, thyroxine; TRα, thyroid receptor alpha; TRβ, thyroid receptor beta; TSH, thyrotropin; WMI, white matter injury.

http://dx.doi.org/10.1016/j.neuroscience.2014.04.038
0306-4522/

of many third world countries [see Fig. 3 in Blencowe et al. (2012)], likely reflecting a variety of socio-economic, lifestyle and healthcare delivery challenges, but critically highlighting the epidemic of preterm birth with resultant neurological disabilities in the United States. While much has been learned about potential etiologies and proposed molecular mechanisms for WMI in the last 20–30 years, the absence of any definitive therapeutic interventions highlights the importance of further studies for this costly and debilitating disorder.

As our knowledge of the neuropathology of brain injury in the premature infant has progressed, the patterns of injuries have evolved to include neurons and axons as well as white matter. The term "encephalopathy of prematurity" has been coined to highlight that the injury involves more than just the myelin (Volpe, 2005, 2009). Several recent reviews (Volpe, 2009; Volpe et al., 2011; Kinney and Volpe, 2012) highlight the importance of areas beyond white matter. Given the breadth of this topic, we will limit our discussion to white matter pathology, although it is critical to recognize the interplay between neuronal/axonal injury and the pathogenesis of WMI (Volpe, 2009). This review will trace the history of white matter pathology in the preterm infant, briefly discuss proposed etiologies, present an overview of relevant animal models, and then discuss our hypothesis that nutritional and hormonal deprivation may be playing an important and overlooked role in white matter pathology.

HISTORY OF PERIVENTRICULAR LEUKOMALACIA (PVL)

The origins of neonatal white matter research can be traced to Banker and Larroche in the 1960s who described a large number of primarily premature infants with unique lesions of the white matter consisting of coagulative necrosis, astrocytic proliferation and microglia activation which they termed "PVL" (Banker and Larroche, 1962). Careful review of the clinical history of these infants showed that all had suffered an anoxic episode and they noted that the areas of injured white matter were found at arterial border zones, supporting their hypothesis that blood with either a lack of oxygen or an excess of oxygen contributed to the pathogenesis of the observed injury. (Of interesting historical note, they also mention that no experimental animal model had reproduced the findings observed in PVL.) An alternative hypothesis implicating infection as an etiology of WMI initially developed from epidemiological work of Leviton and Gilles showing that gram-negative bacteremia at autopsy was highly associated with perinatal telencephalic leukoencephalopathy (Leviton and Gilles, 1973). Subsequent epidemiological studies and prospective cohort studies have confirmed an association of WMI with infection/inflammation (Nelson et al., 1998; Wu et al., 2003; Stoll et al., 2004; Shah et al., 2008; O'Shea et al., 2013).

The emergence of cranial ultrasonography in the late 1970s provided a "window to the neonatal brain" (Volpe, 1982) and while first used to identify hemorrhage and brain anomalies (Babcock and Han, 1981) was recognized to be sensitive at detecting cystic WMI as well (Dubowitz et al., 1985). As this pattern of brain injury became more recognized, neonatal intensive care units began screening more systematically with routine cranial ultrasounds and cystic PVL lesions were identified. At the same time, neonatal intensive care improved, surfactant for lung development was introduced (~1990) and survival of the very-low-birth-weight infants (< 1500 g) improved (Engle et al., 2008; Halliday, 2008; Volpe, 2008). A reappraisal of the major underlying lesion of PVL demonstrated that a more diffuse lesion with microcystic areas was now the predominant lesion (Miller et al., 2005; Woodward et al., 2006) and often detectable with brain MRI (Maalouf et al., 2001; Inder et al., 2003a,b). Most very-low-birth-weight infants now survive, making autopsy studies challenging and highlighting the importance of neuroimaging in evaluating these infants with the diffuse white matter lesion illustrated here on brain MRI (Fig. 1).

ETIOLOGY: PREMYELINATING OLIGODENDROCYTE (PRE-OL) TARGETED

Despite the shift in the predominance of the lesion type, the main hypothesized etiologies, especially hypoxia–ischemia, remain largely unchanged from the studies described above in the 1960s and 1970s, although the likelihood that an important subset of infants experiences a combined insult, infection/inflammation plus hypoxia–ischemia, is apparent. The target of these upstream injury mechanisms is the oligodendrocyte, the myelin-producing cell of the central nervous system. Oligodendrocytes progress through a well-characterized developmental lineage that can be identified through cell surface antigens recognized by monoclonal antibodies A2B5, O4, and O1 as well as antibodies against myelin basic protein (MBP). Oligodendrocyte progenitors express the A2B5 antigen, pre-oligodendrocytes express the O4 antigen, immature, post-mitotic oligodendrocytes express the O1 antigen in addition to the O4 antigen, and mature oligodendrocytes express MBP (Fig. 2). Extensive investigation using oligodendrocyte cultures, pre-clinical animal models and human autopsy material have identified the O4-positive pre-OL as the predominant form of the oligodendrocyte lineage in the human premature brain and the vulnerable cell population leading to WMI [reviewed in Volpe et al. (2011)]. A variety of downstream mechanisms including excitotoxicity, oxidative/nitrative injury from free radicals, and microglial activation have all been implicated in pre-OL injury and death [see comprehensive reviews in Back and Rosenberg (2014) and Rosenberg (2014)]. More recent evidence suggests that following pre-OL injury there is replenishment of the pre-OL pool, but critically, a subsequent failure of proper oligodendrocyte maturation (Billiards et al., 2008; Buser et al., 2012). There has been some suggestion that hyaluronan digestion product accumulation (Preston et al., 2013) may contribute to this maturational block that ultimately leads to hypomyelination.

MODELING WMI IN THE LABORATORY (PRE-CLINICAL MODELS)

Based on the hypotheses that hypoxia–ischemia and inflammation play critical upstream roles in the

Please cite this article in press as: Elitt CM, Rosenberg PA. The challenge of understanding cerebral white matter injury in the premature infant. Neuroscience (2014), http://dx.doi.org/10.1016/j.neuroscience.2014.04.038