White Matter Injury in Premature Newborns

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Abstract

Preterm newborns are highly susceptible to brain injury. White matter injury is among the dominant patterns of brain injury in preterm newborns. The purpose of this review is to discuss the pathogenesis, diagnosis, management, and prevention of white matter injury in premature newborns. The long-term outcome of white matter injury in children born prematurely is also addressed.

Keywords: white matter injury; prematurity

Currently, 11.4 percent of all births in the United States are premature (<37 weeks gestation), and 3.4 percent are born prior to 34 weeks gestation.1 Prematurity is associated with an increased risk of motor, cognitive, and behavioral deficits.2–6 The risk of long-term neurodevelopmental deficits is inversely proportional to gestational age and is highest among the subgroup of newborns that are ,28 weeks gestation at birth.4–6

The developing brain is highly susceptible to injury, particularly to the white matter.2 White matter injury (WMI) is one of the dominant patterns of brain injury in premature newborns.2,3,7,8 Although there has been a decline in WMI over the past two decades,7–9 it remains among the main causes of motor and cognitive disability in children born prematurely.3,6,7,10 The purpose of this review is to discuss the pathogenesis, diagnosis, prevention, and management of WMI in premature newborns. The relationship between WMI and neurodevelopmental outcome in children born prematurely will also be discussed.

Brief Overview of Neuroanatomy

The brain consists of the cerebral hemispheres, cerebellum, and brainstem. Each of these structures is made of gray matter and white matter. The gray matter, or cortex, contains billions of neurons that comprise interconnected networks to control movement, sensation, language, and thought.11 Axons of neurons branch out to connect to other neurons, enabling communication through chemical and electrical signals. The white matter is made of myelinated and unmyelinated axons. Myelin is a fatty insulating substance that allows for more efficient electrical conduction along axons.11 The preterm brain is predominantly unmyelinated. Myelination of the brain proceeds in a developmentally regulated pattern and is largely completed by two years of age.2 Injury to the white matter interrupts the transmission of signals between neurons and can result in motor, cognitive, behavioral, and visual deficits.7

Pathogenesis and Risk Factors of White Matter Injury

The immature white matter in preterm newborns is highly vulnerable to hypoxia, ischemia, and inflammation.2,7,12 These insults lead to the activation of microglia, excitotoxicity, and the generation of free radicals, and these cascades of events converge on selectively vulnerable premyelinating oligodendrocyte cells in the developing white
matter, resulting in cell maturation arrest, cell death, and myelination failure.\textsuperscript{7,12}

WMI encompasses a spectrum of cystic and noncystic injury of which cystic injury is most severe.\textsuperscript{2,3,7,12} Cystic WMI, or cystic periventricular leukomalacia, refers to microscopic areas of coagulation necrosis and liquefaction in the periventricular white matter, which evolve into multiple cysts.\textsuperscript{2} Noncystic WMI is characterized by microscopic focal areas of necrosis that can be ischemic or hemorrhagic in origin.\textsuperscript{2} In postmortem studies of preterm newborns, the incidence of WMI varies widely, and the risk is reported to be highest when intraventricular hemorrhage is also present.\textsuperscript{13–15} Neuropathologic studies also reveal evidence of neuronal loss and gliosis in the cerebral cortex, thalamus, and basal ganglia in premature infants with WMI.\textsuperscript{15}

Clinical risk factors for WMI relate to hypoxia-ischemia and/or inflammation.\textsuperscript{7,12} Premature newborns are predisposed to cerebral ischemia because of a combination of the vascular anatomy, which consists of arterial border zones within the white matter, as well as an impaired ability to auto-regulate cerebral blood flow.\textsuperscript{7,16–18} Because premature newborns are unable to regulate cerebral blood flow in response to changes in systemic blood pressure, cerebral perfusion in premature newborns is pressure-passive.\textsuperscript{18} Hypotension and even small decreases in systemic blood pressure can result in ischemia to the arterial border zones in preterm newborns.\textsuperscript{7} Other risk factors for WMI include infection (e.g., chorioamnionitis, sepsis, meningitis), necrotizing enterocolitis, hypocarbia, hyperoxia, and hypoxia, as well as prolonged mechanical ventilation and chronic lung disease.\textsuperscript{7,9,19–25} For a detailed discussion of the pathogenesis of WMI, please see the review article by Khawaja and Volpe.\textsuperscript{7}

**DIAGNOSIS OF WHITE MATTER INJURY**

Cranial ultrasound is the main imaging modality used to routinely diagnose WMI in preterm newborns.\textsuperscript{10} Ultrasound has a high sensitivity for the detection of cystic lesions (Figure 1); however, magnetic resonance imaging (MRI) is superior for the detection of more subtle, noncystic lesions (Figure 2).\textsuperscript{26–28}

Cystic WMI undergoes a characteristic pattern of evolution. After a known acute insult, areas of increased echogenicity are seen on ultrasound within four to seven days following the insult and develop into cystic lesions after two to four weeks.\textsuperscript{2,29,30} Cysts are usually only visible for a few weeks on cranial ultrasound. Consequently, sequential ultrasounds are important for the detection of cystic injury, in particular following acute illness later in the neonatal period, such as sepsis or acute hypoxia-ischemia.\textsuperscript{29} After cysts have resolved, ventricular dilatation may be seen because of atrophy of the periventricular white matter.\textsuperscript{29,30}

Several studies have compared ultrasound and MRI for the diagnosis of WMI in preterm newborns.\textsuperscript{10,26–28} The improved resolution of MRI allows for better determination of the site and extent of focal noncystic WMI. The severity of noncystic WMI can be graded according to the number, size, and extent of focal areas of injury (see Figure 2).\textsuperscript{26} Less than 20 percent of preterm newborns imaged with MRI at term-equivalent age have moderate to severe WMI.\textsuperscript{9,10} Foci of WMI can also be visualized on MRI soon after birth.\textsuperscript{2,26} Progressive WMI on serial MRI soon after birth and near term-equivalent age is more common in newborns with chronic lung disease and recurrent postnatal infections.\textsuperscript{20}

The incidence of cystic WMI has declined over recent decades and is now <1 percent in some studies.\textsuperscript{8,31} Hamrick and colleagues demonstrated that cystic WMI decreased significantly in their cohort of preterm infants evaluated with ultrasound from 1992 to 2002;\textsuperscript{8} however, there was not a significant change in periventricular hemorrhagic infarction over time. They also found that a proportion of the decline in cystic WMI in their cohort could be attributed to a concurrent decrease in the duration of mechanical ventilation.\textsuperscript{8} We have recently shown that the rate of MRI-detected WMI decreased in a cohort of preterm newborns studied between 1998 and 2011, even accounting for differences in the clinical predictors of WMI over the study period.\textsuperscript{9} Taken together, these studies suggest that both cystic and noncystic WMI have decreased over the past two decades. We hypothesized that unmeasured changes in clinical care, such as noninvasive mechanical ventilation, feeding, and handling practices, may have led to a reduced cumulative incidence of recurrent hypoxic-ischemic insults, which in turn translated into a decreased burden of WMI. Further study will help clarify which changes in clinical care are associated with a reduction of WMI.

Current recommendations of the American Academy of Neurology and Child Neurology Society suggest cranial
ultrasound be performed for all infants <30 weeks gestation between Days 7 and 14 of life, and optimally ultrasound should be repeated again between 36 and 40 weeks postmenstrual age. Because MRI is superior to ultrasound for the detection of milder forms of injury, it is considered to be more reliable for neurodevelopmental prognosis in preterm infants. However, there is a lack of consensus regarding the role of routine MRI scans in preterm newborns and the optimal timing of MRI for prognostication of neurodevelopment.

MANAGEMENT OF WHITE MATTER INJURY

Management of WMI in premature newborns is supportive and largely consists of the prevention and treatment of the clinical risk factors associated with WMI, for example, treatment of hypotension and maintenance of cerebral perfusion as well as treatment of infection. There are no established pharmacologic treatments to alleviate the effects of WMI. Because MRI is associated with an increased risk of neurodevelopmental deficits, infants diagnosed with WMI should be evaluated by occupational and physical therapy in the NICU and referred to an early developmental intervention program upon discharge. Surveillance of development and learning throughout childhood enables the provision of occupational, physical, and/or speech therapy, as well as learning supports, as needed. Parental counseling and education are also important aspects of management.

PREVENTION OF WHITE MATTER INJURY

There are no established therapies to prevent WMI. Antenatal therapies commonly given to women at risk of preterm birth, such as magnesium sulfate, are not associated with a reduction of WMI, although corticosteroids may mitigate upstream mechanisms of ischemia to indirectly prevent WMI. Some observational studies have shown a reduced risk of WMI in premature newborns with prolonged exposure to indomethacin (>3 doses); however, a randomized controlled trial is needed to determine if indomethacin can effectively prevent WMI. The potential mechanisms by which indomethacin may reduce WMI include anti-inflammatory effects, as well as widening the range of cerebral vascular autoregulation and decreasing cerebral blood flow.

Other potential neuroprotective therapies that have been proposed include nutritional supplementation to reduce systemic infections and modulate the immune response. Although there have been no studies that have evaluated the impact of nutritional supplementation on the risk of WMI, one randomized trial of glutamine supplementation in newborns showed that glutamine was associated with improved microstructural integrity of the white matter on advanced quantitative MRI. In addition, medications such as erythropoietin, melatonin, and caffeine have been proposed as potential preventative interventions because they have multiple downstream effects on the cascade of events by which excitotoxicity results in injury.

From the nursing perspective, there are no specific strategies at the bedside that have been shown to prevent WMI. However, as bundles of care for the prevention of intraventricular hemorrhage become more widely implemented, components such as minimizing handling and clustering touch times may in turn have a beneficial effect on the risk of WMI.

FIGURE 2: Noncystic white matter injury.

Coronal T1-weighted magnetic resonance imaging scans illustrating hyperintense foci of injury (white arrows): (a) mild (=3 foci each ≤2 mm), (b) moderate (>3 foci each ≤2 mm, or any focus >2 mm), and (c) severe (>5% hemispheric white matter injured) noncystic WMI.
WHITE MATTER INJURY AND LONG-TERM OUTCOME

WMI is associated with abnormalities in motor development, such as cerebral palsy, as well as cognitive deficits. Motor deficits can range from subtle incoordination and abnormalities in tone and strength that are not functionally limiting, to functionally disabling cerebral palsy. Intellectual disability can also range in severity. In addition, studies have demonstrated an association between WMI in preterm newborns and an increased risk of neurocognitive and behavioral deficits including inattention and executive dysfunction.

Recently, a large multicenter study conducted by the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network compared the prognostic value of serial cranial ultrasound and near-term MRI in preterm newborns. The authors found that both ultrasound and MRI obtained near term-age were predictive of adverse outcome at 18–22 months corrected age. Importantly, this study also emphasized that a proportion of newborns with WMI diagnosed near term-equivalent age did not have severe adverse outcomes, which highlights that factors in addition to WMI must be taken into account for prognostication of neurodevelopment in early childhood. These factors may include birth weight, gestational age, gender, and illness severity, as well as weight gain in early infancy, socioeconomic status, and maternal education. Other forms of brain injury such as intraventricular hemorrhage and cerebellar injury also need to be considered when prognosticating neurodevelopment.

CONCLUSIONS

Preterm newborns are highly susceptible to WMI because of a developmental vulnerability to conditions such as hypoxia, ischemia, and inflammation. Cranial ultrasound and MRI can be used to diagnose WMI; however, MRI is superior for the detection of more subtle forms of injury. Currently, there are no established therapies for the prevention or treatment of WMI. A comprehensive interdisciplinary health care team is needed to support infants with WMI in the NICU and prepare for discharge. Rehabilitative interventions and learning supports play an important role in the long-term management of preterm infants with WMI.

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Dawn Gano, MD, is a child neurologist who specializes in the diagnosis and management of brain injury and neurologic disorders in newborns. Her research focuses on the promotion of brain health in premature newborns through the identification of modifiable risk factors for brain injury and adverse neurodevelopment.

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