REVIEW ARTICLE

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Defining the Neurologic Consequences of Preterm Birth

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Globally, an estimated 15 million infants are born preterm (at <37 weeks' gestation) each year,[1] and prematurity is the leading cause of neonatal death. For survivors of preterm birth, the risk of long-term disorders, particularly neurologic and developmental disabilities,[2] remains high, despite advances in perinatal health care. Over the past two decades, the incidence of cerebral palsy, particularly severe cerebral palsy, has declined.[3,4] However, there has been no decline in the high incidence of cognitive impairment and social and emotional challenges among children and young adults born preterm.[4,5] At a group level, the mean (±SD) IQ of very preterm children (those born at <32 weeks' gestation) is 11 to 12 points (±0.7 to 0.8) lower than that of infants born at term,[6] with deficits in IQ increasing to 15 to 20 points for those born at less than 26 weeks' gestation.[7] At an individual level, the long-term outcome for very preterm children varies greatly, with a proportion of such children free of any neurodevelopmental impairment. This heterogeneity in neurodevelopmental outcomes is likely to reflect the nature and severity of brain injury and dysmaturation after preterm birth, with infants born at the earliest gestational ages at greatest risk.

The immature brain is vulnerable to unique forms of brain injury, including white-matter injury, germinal matrix–intraventricular hemorrhage, and cerebellar hemorrhage. New insights from advanced neuroimaging techniques, complemented by progress in developmental neuroscience, have expanded our knowledge about both the nature of the primary injury and the secondary dysmaturational effects. Although the major forms of brain injury have adverse neurodevelopmental outcomes, recent recognition of altered brain development in preterm infants has provided a new understanding of key factors during the period spent in the neonatal intensive care unit (NICU) that may modulate this critical phase of rapid brain development, with adverse neurodevelopmental consequences. Thus, not only brain injury but also impaired brain development, due to and potentially independent of injury, contribute to adverse neurodevelopmental consequences in preterm infants.

This review outlines the three major forms of brain injury in very preterm infants, the nature of the alterations in subsequent brain development (dysmaturation), the factors that may mediate these alterations, and their neurodevelopmental consequences. An understanding of these factors will assist neonatal clinicians in using future neuroprotective strategies to improve long-term neurologic outcomes in the preterm infant (Fig. 1 and Table 1).

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BRAIN INJURY

Three major forms of recognized brain injury in preterm infants are associated with subsequent neurodevelopmental impairment: white-matter injury, germinal matrix–

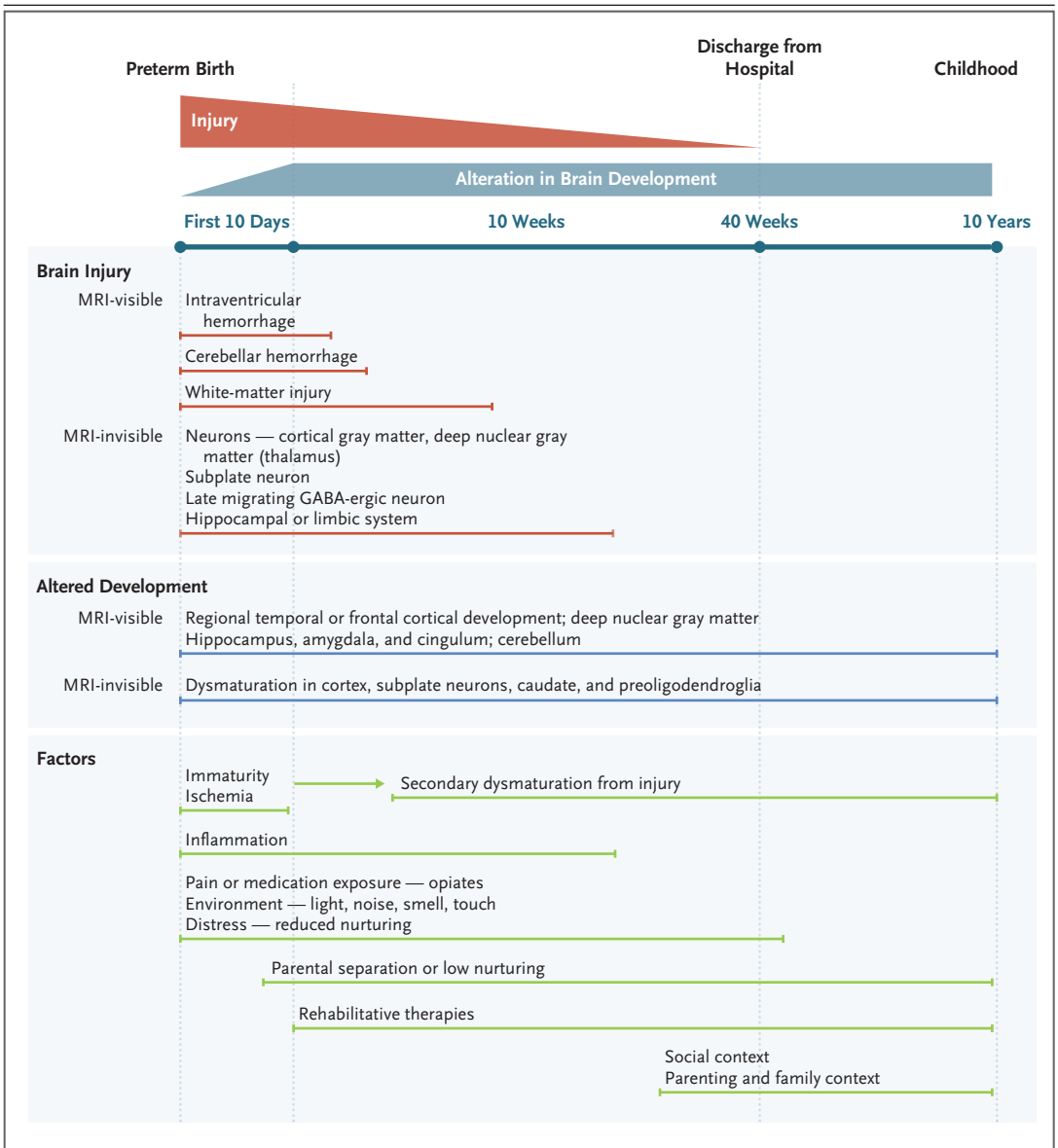

Figure 1. Timeline of Vulnerability or Exposure and Neurologic Consequences of Preterm Birth.

Shown are the key timing, patterns, and factors determining the neurologic consequences of preterm birth. GABA denotes γ-aminobutyric acid, and MRI magnetic resonance imaging.

intraventricular hemorrhage, and cerebellar hemorrhage.

WHITE-MATTER INJURY

Among the injuries affecting the developing preterm brain, white-matter injury is the most prevalent, owing to the exquisite vulnerability of early differentiating preoligodendrocytes. The key risk factors leading to white-matter injury include hypoxia–ischemia and inflammation, the latter often related to perinatal and neonatal infection.[8] The period from 23 to 32 weeks' gestation constitutes the period of highest risk for white-matter injury, peaking at 28 weeks' gestation.[9] White-matter injury comprises three major pathological forms — focal cystic necrosis, focal microscopic necrosis, and diffuse non-necrotic lesions — each accompanied by diffuse gliosis (reactive astrocytes and activated microglia)[8] (Fig. 2). The cystic form of white-matter injury,

Table 1. Evidence of Association of Brain Injury and Dysmaturation with Functional Impairment in Preterm Infants and Potential Interventions to Improve Outcomes.*

Functional Impairment	Brain Injury				MRI-Defined Brain Dysmaturation		
	High-Grade Intraventricular Hemorrhage	Cystic White-Matter Injury	Diffuse White-Matter Injury	Cerebellar Hemorrhage	Frontal or Temporal Region	Basal Ganglia or Thalamus	Cerebellum
Early development	Strong	Strong	Strong	Moderate	Moderate	NC	Moderate
Motor function	Strong	Strong	Moderate	Strong	ND	Moderate	Moderate
IQ	Strong	Strong	Moderate	Strong	Moderate	Moderate	Moderate
Language	Moderate	Strong	Moderate	Moderate	Moderate	NC	Moderate
Visuospatial function	Moderate	Strong	Moderate	Weak	NC	NC	Weak
Memory	Moderate	Moderate	Moderate	NC	Moderate	Moderate	Weak
Attention and executive function	Moderate	Moderate	Moderate	NC	Moderate	Weak	Weak
Academic performance	Moderate	Strong	Moderate	NC	NC	Moderate	NC
Behavior	Moderate	Moderate	Moderate	Moderate	NC	Moderate	Moderate
Interventions	Antenatal glucocorticoids, magnesium sulfate, delayed cord clamping NICU: physiological stability — prevent fluctuations in carbon dioxide, glucose, blood pressure Cerebrovascular monitoring to ensure stable cerebral perfusion Neurorehabilitation with parent–infant interaction and infant developmental therapy				Provide appropriate nutrition: macronutrients and micronutrients, maternal breast milk Minimize distress and stressful or painful experiences Enhance nurturing: skin-to-skin care, parental presence and engagement, exposure to human voices Home-based developmental programs		

* Evidence is classified as strong, meaning that there is well-established evidence of a relationship; moderate, meaning that there is evidence of a relationship but that more research is needed; or weak, meaning that there is inconsistent evidence. MRI denotes magnetic resonance imaging, NC no clear evidence, ND not determined, and NICU neonatal intensive care unit.

which is the most severe, affects less than 5% of preterm infants born before 32 weeks' gestation.[9,10] Microscopic focal necroses, usually visible on magnetic resonance imaging (MRI) as punctate white-matter lesions, are reported in 15 to 25% of extremely preterm infants (born at <28 weeks' gestation). Diffuse, non-necrotic lesions with gliosis, associated with less visible abnormalities on MRI but often followed by diminished white-matter volume and ventriculomegaly, occur in nearly half of very preterm infants.[9,11-14]

The incidence of cystic white-matter injury in preterm infants is low and declining,[9,10] possibly reflecting more widespread antenatal glucocorticoid use in mothers at risk for premature delivery.[15,16] Cystic white-matter injury is associated with clinically significant developmental impairment (Table 1). Cerebral palsy develops in approximately 75% of infants with cystic white-matter injury. Half of affected infants have impairment in general cognition and vision, and 25% have a seizure disorder.[17,18] In contrast, punctate white-matter lesions and diffuse, non-necrotic white-matter injury have been associated with lower IQ and academic functioning, with an increased risk of impairment in motor function, attention, information processing, language, memory and learning, and executive function.[12,19,20]

GERMINAL MATRIX–INTRAVENTRICULAR HEMORRHAGE

Germinal matrix–intraventricular hemorrhage is the most common form of neonatal intracranial hemorrhage and is characteristic of central nervous system bleeding in preterm infants. This form of brain injury affects approximately 25% of all preterm infants with very low birth weight (<1500 g).[21] Despite advances in perinatal care, the incidence has not changed in the past two decades.[5,10] The importance of such lesions relates not only to their high incidence but also to the gravity of the more severe forms of intraventricular hemorrhage and their attendant complications. The severity of intraventricular hemorrhage, classified with the use of a grading system (grades 1 through 4) first reported by Papile and

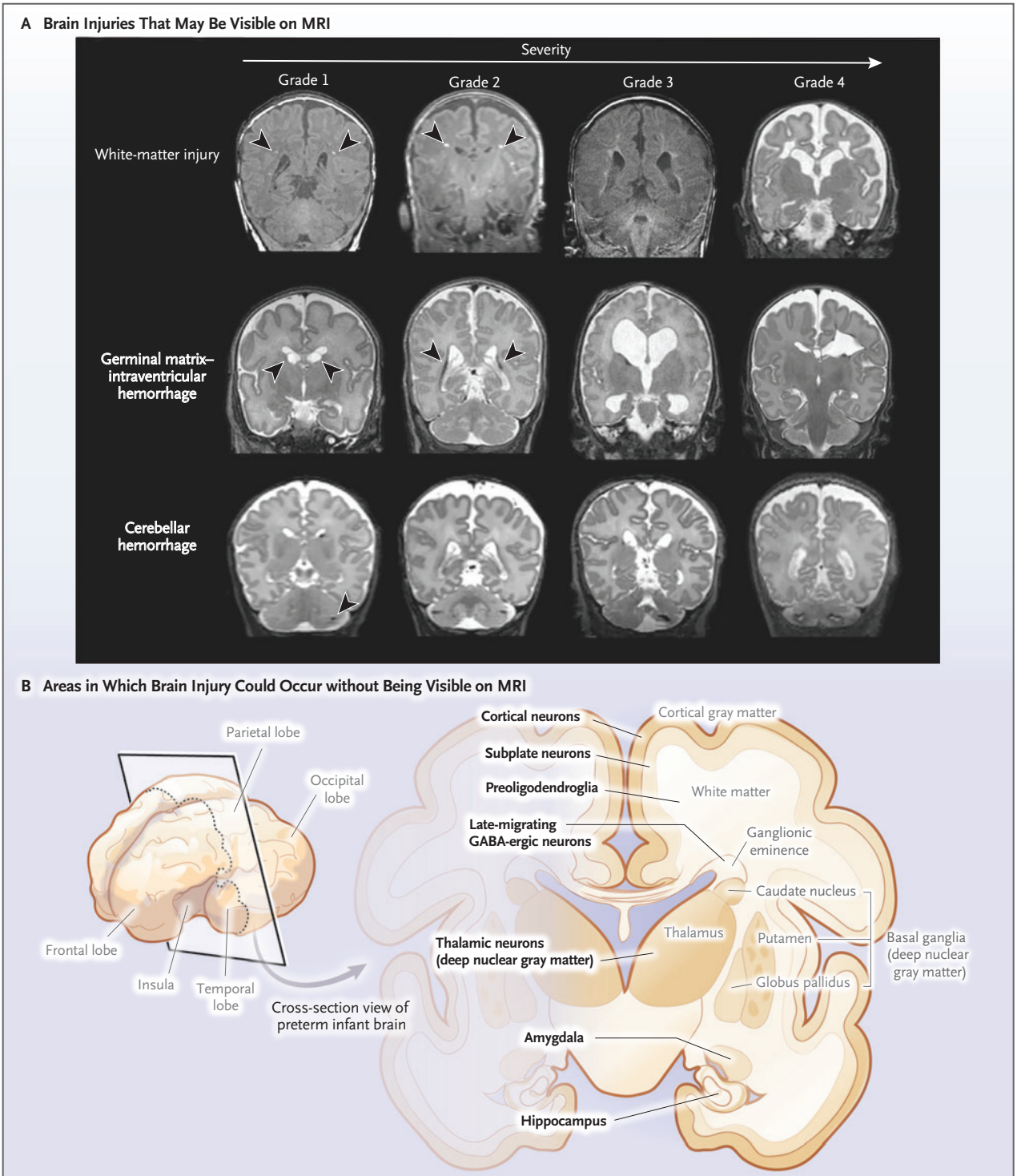

Figure 2. Patterns of Brain Injury.

Forms of injury that may be visible on MRI include white-matter injury, germinal matrix–intraventricular hemorrhage, and cerebellar hemorrhage (Panel A). Arrowheads denote focal areas of injury. The severity of the injury is graded from 1 (mild) to 4 (severe). Injury that is not visible on MRI also occurs in many neuronal regions (Panel B).

colleagues in 1978 and later modified,[22,23] is based on the amount of blood in the lateral ventricles and cerebral parenchyma. Studies using serial cranial ultrasound imaging have shown that the onset of germinal matrix–intraventricular hemorrhage occurs at a mean of 24 to 48 hours after delivery, with approximately 10% of cases developing within 12 hours after birth[24] (Figs. 1 and 2). Clinical signs do not play a major role in the diagnosis of germinal matrix–intraventricular hemorrhage; most cases are silent at the time of occurrence.

The pathogenesis of germinal matrix–intraventricular hemorrhage often involves complex interactions of multiple factors in the individual infant. Cerebrovascular factors relating to the stability of cerebral blood flow are particularly relevant. In the extremely preterm infant, immature cerebral autoregulation during a period of major cardiorespiratory instability can result in both ischemic and reperfusion insults that injure the fragile germinal matrix vessels, with subsequent rupture and hemorrhage. Evidence-based interventions to reduce the incidence of germinal matrix–intraventricular hemorrhage are limited because of the complexity of the etiologic factors and the current limitations in methods for accurately and continuously measuring cerebral blood flow.

The occurrence of germinal matrix–intraventricular hemorrhage affects subsequent brain development in multiple ways. Consequences may include destruction of the immature germinal cerebral region, resulting in loss of progenitor cells; compression of terminal veins, which can result in high-grade parenchymal venous hemorrhagic infarction; acceleration of white-matter injury through oxidative stress; and hydrocephalus, which can follow intraventricular hemorrhage and lead to axonal and other injuries.

Germinal matrix–intraventricular hemorrhage is categorized as low grade (grade 1 or 2) or high grade (grade 3 or 4). Low-grade germinal matrix–intraventricular hemorrhage has been considered historically to have minimal long-term neurodevelopmental consequences.[25,26] However, large geographic cohort studies involving very preterm and extremely preterm infants have shown that low-grade intraventricular hemorrhage is associated with a small increase in the risk of cerebral palsy and a marked increase in early cognitive delay and visual impairment.[21,27] Evidence of long-term impairment after low-grade intraventricular hemorrhage remains limited, with one study showing no effect on outcomes at 8 and 18 years.[28] In contrast, high-grade intraventricular hemorrhage is associated with a high risk of neurodevelopmental impairment (Table 1). In early childhood, children who had high-grade intraventricular hemorrhage in infancy are 6 times as likely to have cerebral palsy, 11 times as likely to have a visual impairment, and 4 times as likely to have bilateral hearing loss as those who did not have intraventricular hemorrhage.[21] Consequences of high-grade intraventricular hemorrhage that are observed in later childhood include low IQ and academic achievement, as well as deficits in language, attention, working memory, processing speed, visuospatial reasoning, visuomotor integration, and executive function.[26,29]

CEREBELLAR HEMORRHAGE

As with intraventricular hemorrhage, the susceptibility to cerebellar hemorrhage in preterm infants is related to several maturation-dependent vascular regions. These regions include the germinal matrixes in the external granular-cell layer and subependymal region of the cerebellum and a region of rapid growth at the junction of the developing inner granular-cell layer and cerebellar white matter. These regions are vulnerable to ischemic–reperfusion injury and rupture.[30] The assessed incidence of cerebellar hemorrhage depends on the method of assessment. Cerebellar hemorrhage was initially reported in only 3% of preterm infants (born at <30 weeks' gestation) when hemorrhage was assessed by means of cranial ultrasonography through the anterior fontanel,[31] but the incidence rose to 9% when the assessment was based on ultrasonography through the mastoid fontanel windows and to 19% when MRI was used.[32] Pathogenic factors in cerebellar hemorrhage overlap greatly with those in germinal matrix–intraventricular hemorrhage. The most prominent factors are immaturity and cardiorespiratory instability. Injury from cerebellar hemorrhage ranges from unilateral punctate hemorrhage to extensive bilateral lesions[33] (Fig. 2).

The outcome for children with extensive cerebellar hemorrhage is often poor[34] (Table 1), but determining the independent contribution of the cerebellar hemorrhage can be challenging be-

cause it often coexists with supratentorial lesions.[35] In a review of isolated cerebellar hemorrhage, a high incidence of delay in cognitive development (38%), motor function (39%), language (41%), and behavioral development (38%) was reported.[36] The location and size of the lesions contribute to the functional outcome.[37] The long-term outcome for infants with small lesions remains unclear.

BRAIN DYSMATURATION

It has become increasingly clear that the adverse neurodevelopmental consequences of preterm birth are mediated by both the initial brain injury and the subsequent adverse effect of this injury on the development of both white and gray matter, referred to as dysmaturation. This unique vulnerability in the preterm brain is due to the multiple rapid and complex developmental cellular events occurring in the immature cerebrum from 20 to 40 weeks' gestation. In this section, we review the definition of brain dysmaturation in the preterm infant as delineated by MRI and the primary mechanism of dysmaturation due to white-matter injury, as well as evidence supporting primary dysmaturational effects of adverse exposures in the NICU. Finally, we summarize the literature on the developmental consequences of brain dysmaturation (Table 1). Since these dysmaturational cellular mechanisms appear to occur over a relatively long period, not just during the NICU stay, interventions in the NICU and after discharge that are designed to prevent or ameliorate dysmaturation seem plausible (Table 1). Whether the absence of any in utero factors, such as neurohormones, might have a role remains unknown.

IDENTIFYING BRAIN DYSMATURATION IN VIVO

The principal manifestations of dysmaturation in the preterm brain have been elucidated in living infants with the use of several MRI techniques. Volumetric MRI shows abnormalities as diminished regional volumes of the cerebral cortex, white matter, thalamus, and basal ganglia (Figs. 3 and 4). Diffusion-based imaging shows cerebral white matter with decreased fractional anisotropy (a measure of connectivity within the brain) and relatively greater involvement of radial diffusivity (which is consistent with impaired preoligodendrocyte ensheathment of axons), with cerebral cortical blunting of the normal decline in fractional anisotropy (which is consistent with impaired dendritic development). Surface-based MRI measures show decreased cerebral cortical surface area and cortical folding, or gyrification (Fig. 4A and B), and functional MRI shows impaired connectivity, especially thalamocortical connectivity. There appear to be specific neuronal populations and regions in the immature brain that are most vulnerable (Figs. 3 and 4), such as the thalamus, frontotemporal cortical gray matter, and the limbic regions. Although these abnormalities have been defined at term-equivalent ages, they persist, or their manifestations may increase in later infancy, childhood, adolescence, or adulthood.[38-43]

DYSMATURATION DUE TO WHITE-MATTER INJURY

The neuropathological consequences of injury to preoligodendrocytes in immature white matter include failure of maturation to myelin-producing oligodendroglia, resulting in hypomyelination. A secondary form of dysmaturation can follow white-matter injury and involve an array of developmental events that are active in cerebral white- and gray-matter structures during the preterm period. This evolution begins with the failure of preoligodendrocyte maturation and its ensheathment of axons, thereby causing, through anterograde and retrograde mechanisms, impairment of neuronal and axonal maturation. This combination of white-matter injury and secondary disturbances of gray-matter structures has been termed the "encephalopathy of prematurity."[44] The likely mechanisms that lead to impaired maturation of neuronal and axonal structures have been reviewed elsewhere.[8]

PRIMARY NEURONAL DYSMATURATION

Clinical and experimental studies have suggested that altered neuronal maturation may be a primary event in the immature brain, distinct from the dysmaturation due to white-matter injury. This notion was supported by a study using diffusion-based MRI in preterm infants at two time points during hospitalization.[45] The principal finding was an impairment in the expected maturational decline in fractional anisotropy in the cortex without evidence of white-matter injury, which is consistent with a delay in the microstructural development of the cortical gray matter. Anisotropy measures are known to decrease in the developing cortex, principally with

dendritic elaboration,[46,47] which suggests that the findings of this study indicate a primary impairment in the dendritic development of cortical gray matter. Definitive neuropathological evidence of primary neuronal dysmaturation has not been shown in clinical studies.

Observations in a study of an immature ovine model also suggest a primary impairment of cortical neuronal development. That study showed that relatively brief, isolated hypoxia resulted in altered dendritic arborization within the hippocampus, accompanied by impaired connectivity and altered working memory.[48] The latter observation may be relevant, since disturbances in working memory have commonly been reported in survivors of very preterm birth.[49] Additional studies in this model have shown hypoxia and ischemia, resulting in disruption of neuronal development.[50]

In addition to hypoxia, other factors are likely to mediate disturbances in the development of both gray and white matter in preterm infants during the NICU stay, including nutrition and growth, as well as negative experiences (pain, stress, and exposure to harsh light or sound) and the absence of positive experiences (nurturing, exposure to human voices, and healing touch).[8,51] However, separating a primary dysmaturational effect of these factors from a neuromodulatory effect on dysmaturation after injury, particularly white-matter injury, is challenging.

CORRELATIONS OF BRAIN DYSMATURATION WITH OUTCOMES

Associations between cerebral dysmaturation and neurodevelopmental outcomes are often confounded by the underlying injury, particularly white-matter injury. The documented reductions in cerebral cortical volumes in preterm infants at the time of discharge from the NICU have been reported to have variable relationships to outcomes, although attempts to individualize volumetric comparisons may improve prediction.[52] Alterations in regional volumes in children born preterm, as compared with those born at term, can be related to specific later outcomes, such as socioemotional development.[53]

With regard to cortical surface area, regional

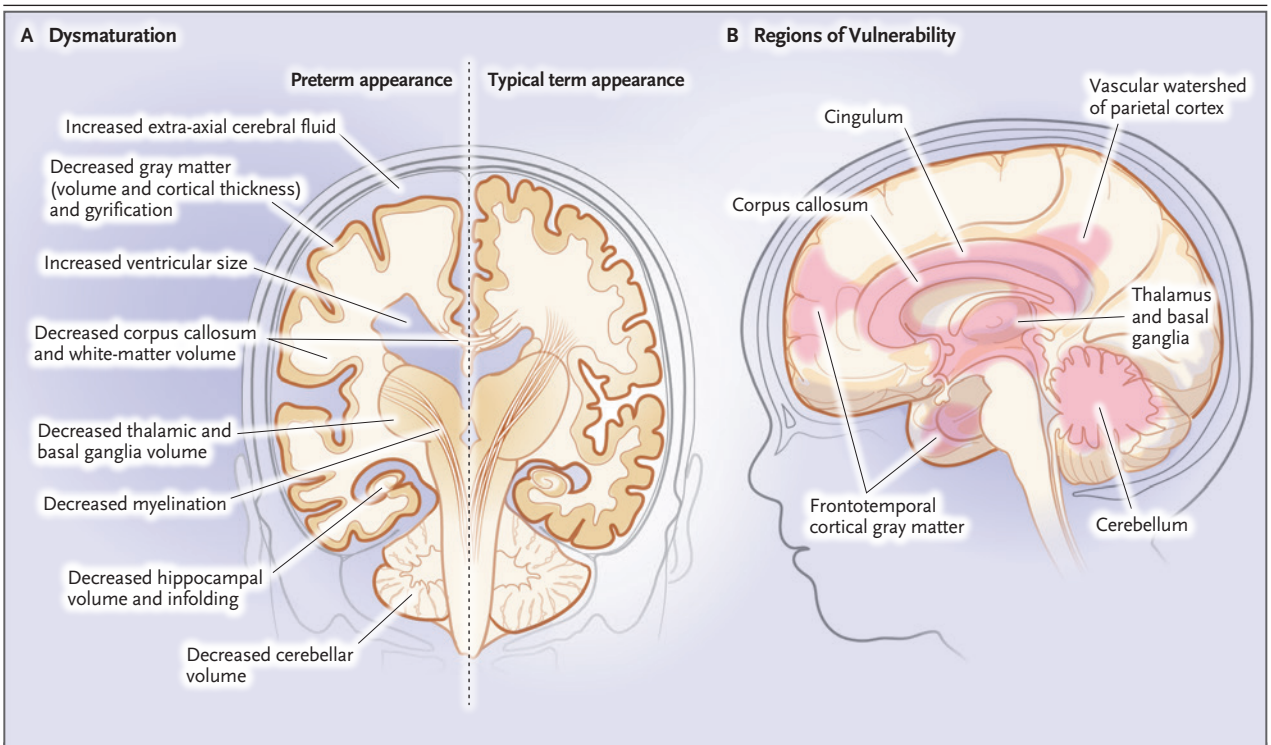

Figure 3. Dysmaturation of the Premature Brain as Seen on MRI.

Panel A shows the brain in a preterm infant as compared with the brain in an infant born at term. Regions of vulnerability are shown in Panel B.

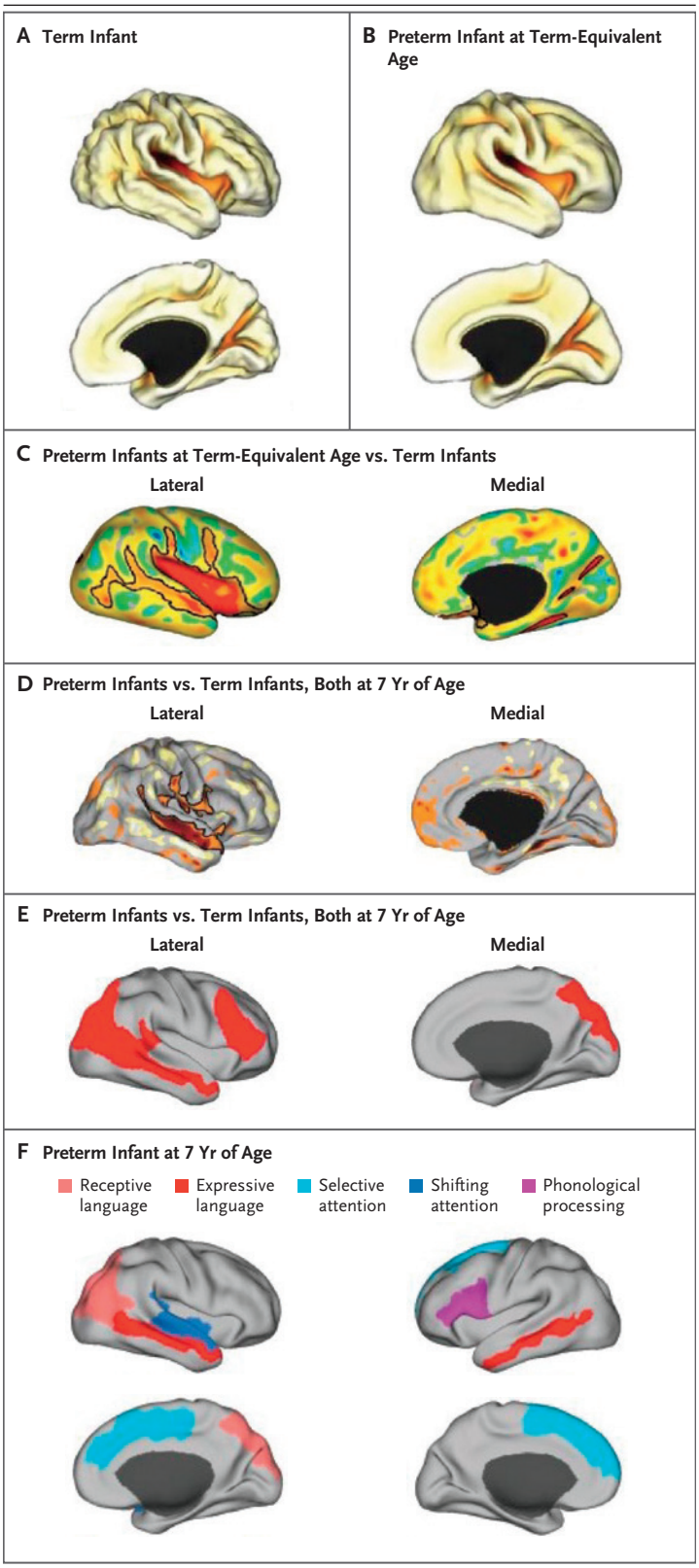

Figure 4. Visible Alterations in Cortical Structure at Term-Equivalent Age and at 7 Years and the Association between Reduced Brain Volume and Impaired Performance.

Shown are representative images of the mean cortical thickness in the left hemisphere in an infant born at term (Panel A) and in a preterm infant at term-equivalent age (Panel B). The temporal lobe is smooth in the preterm infant. The t-statistic–based maps of sulcal depth in the left hemisphere (Panel C, lateral view) show regions of significant difference ($P<0.025$)[38] (outlined in black) between preterm and term infants. Similar findings were observed in the right hemisphere (not shown). Yellow and orange areas indicate differences that do not reach statistical significance. At 7 years of age, sulcal depth remains significantly different ($P<0.05$)[38] in the temporal lobe (Panel D, lateral view, areas outlined black). Yellow and orange areas indicate differences that do not reach statistical significance. As compared with infants born at term, preterm infants have corresponding significant reductions in brain volume ($P<0.025$)[38] (Panel E, red). Reduced brain volume in these regions is associated with impaired function in several domains (Panel F).

reductions in the frontal, temporal, and parietal regions in children born preterm, with increased inner cortical curvature (due to shallower sulci in preterm infants), are negatively associated with later cognitive and language development[51] (Table 1). Numerous studies of cortical alterations and functional outcomes in older children and adults born preterm have shown that the prefrontal and temporal regions are particularly vulnerable[54-58] (Figs. 3 and 4). Morphologic alterations in the frontal and temporal regions in children born preterm have been associated with lower IQ, as well as deficits in language and executive function[59,60] (Fig. 4). Within the temporal cortex, the hippocampus has been reported to be smaller and straighter (with less infolding) in persons who were born preterm[55,61] (Fig. 3 and Table 1), findings that have been inconsistently related to memory performance.[55,62]

Concerning subcortical structures, survivors of very preterm birth have a 6 to 10% reduction in basal ganglia and thalamic volumes at term-equivalent age, as compared with children born at term (Fig. 4 and Table 1), and these volume reductions are associated with impairment in school-age functioning, including impairment related to IQ, memory, academic performance, behavior, and motor function.[63] Reductions in deep

gray-matter structures in children born very preterm are associated with poor motor coordination and cognitive and language impairment at 7 years of age[64] (Table 1).

Cerebellar development is also disrupted after very preterm birth. Smaller cerebellar volumes are observed in the neonatal period,[65,66] childhood,[67] and adulthood,[68] with longitudinal analyses showing slower growth during early and later childhood[65,68] (Fig. 3). Reductions in cerebellar volumes in very preterm infants are associated with early signs of neurologic impairment[69] and developmental delay,[70] as well as long-term deficits in IQ, language, and motor function[65] (Table 1). In children, adolescents, and young adults born very preterm, a smaller cerebellum has been linked to lower scores on measures of IQ, working memory, verbal reasoning, visuospatial processing, language, and executive function.[67,68]

INTERVENTIONS TO COUNTERACT BRAIN DYSMATURATION IN PRETERM INFANTS

The possibility that dysmaturation of white- and gray-matter structures, whether directly or indirectly related to brain injury, can be counteracted has been suggested by a variety of clinical, epidemiologic, and experimental studies. Factors that may play a role in counteracting dysmaturation include not only the prevention of hypoxia, ischemia, and inflammatory insults but also nutritional support and a variety of experiential factors (Table 1).

Studies have shown that appropriate nutrition during the preterm period is important for neurodevelopmental outcomes and that postnatal undernutrition is deleterious.[71,72] The prevalence of impaired nutrition among preterm infants during the NICU stay is high. One study showed that 50% of very-low-birth-weight preterm infants had a discharge weight below the 10th percentile for postmenstrual age and that 27% had a discharge weight below the 3rd percentile.[73] Discussion of the importance of specific nutrients is beyond the scope of this review. However, in several studies using volumetric and diffusion-tensor MRI, breast-feeding was shown to be associated with improved white-matter maturation in preterm infants,[74,75] and there is some evidence that higher caloric and lipid intake is associated with less severe brain injury and dysmaturation.[76]

Experiential factors are also likely to play a major role in mediating alterations in brain development during the stay in the NICU. Pain and stress are common experiences for preterm infants in the NICU and have been shown to have adverse effects on neurodevelopmental, behavioral, and cognitive outcomes.[77-79] Abnormalities of brain development associated with pain and stress have involved neuron-rich areas such as the cerebral cortex, hippocampus, and thalamus, as well as functional connectivity among these structures.[80,81] Nonpharmacologic approaches, including sucrose administration, may help reduce the number of painful experiences or modify the stress associated with them.[81] An example of nonpharmacologic stress reduction was demonstrated in a small clinical trial of the Newborn Individualized Developmental Care and Assessment Program (NIDCAP), which aims to modify the infant's environment in order to reduce stress and maximize rest. The trial results revealed higher cortical gray-matter volumes and higher fractional anisotropy in growth-restricted preterm infants who received care in the NIDCAP than in those who received standard care.[82]

Experimental studies suggest that neuronal maturation can be altered by environmental sensory factors, such as auditory and visual input.[83] Historically, the NICU has been a brightly lit environment with excessive noise throughout 24 hours per day of continuous activity. Recent trends in NICU design have led to infants being cared for in single rooms, enhancing privacy for the family and reducing rates of infection.[84] However, both the overstimulation of the historical NICU design and the quiet single-room design may have detrimental effects on brain maturation.

Concerning auditory input, several clinical studies have suggested a modulatory effect of the neonatal auditory environment on cortical neuronal development.[51,85] These studies show a correlation between the auditory environment — with human voices and particularly parental voices — and language outcomes in very preterm infants.

Neonatal visual experience may also play a role in neuronal maturation. Development of the visual cortex is very active during the preterm period and into infancy, and studies in animals have shown that both premature visual stimula-

tion and visual deprivation have dramatic effects on visual development.[8]

Finally, parental and family factors play a critical role in infant development. The socioeconomic status of the family and the level of maternal education have been reported to have a modifying influence on brain development in very preterm infants, with lower socioeconomic status correlated with developmental disturbances of the cerebral cortex, thalamus, and hippocampus.[86] Persistent emotional distress, which is understandably common in parents of very preterm infants,[87] may adversely affect the infant's neurodevelopment.[88] Sensitive and responsive parenting has been associated with better neurodevelopmental outcomes and, for boys, greater growth of basal ganglia and amygdala structures, findings that are possibly related to lower parental distress levels. Intrusive or overcontrolling parental behaviors were reported to be associated with poorer neurodevelopmental outcomes, reductions in gray-matter volume, and delayed white-matter maturity.[89,90]

Given the important role of parenting and the family environment, family-based interventions may well improve the long-term outcome for children born preterm. A Cochrane review of developmental interventions for infants born preterm showed benefits with respect to outcomes in preschoolers. The benefits were most apparent with interventions that commenced in the NICU and included both parent–infant interaction and infant development.[91] The review suggested that the benefits did not persist into school age. However, meta-analyses have also shown that family-based interventions are associated with fewer behavioral problems throughout childhood,[92] as well as reduced anxiety and depressive symptoms in parents.[93]

CONCLUSIONS

An increasing number of infants born very preterm survive the neonatal period but too often have long-term adverse neurologic effects. Although many extremely preterm infants do well, a greater understanding of the mechanisms of adverse outcomes is critical for attaining good outcomes for even more such infants. Adverse outcomes result from a combination of unique forms of brain injury and alterations in brain development. The common forms of brain injury most frequently occur in association with cardiorespiratory instability, without any clinical signs during the first week of life. Future reductions in ischemia–reperfusion brain injury will require technological advances in the monitoring of brain perfusion to inform critical care management. Along with early recognition of brain injury, the use of rehabilitative strategies both during the NICU stay and after discharge may contribute to neurorestoration.

With regard to brain development, systematic investigation must be prioritized. Gaps in knowledge exist regarding the neurobiologic effects of the sensory environment, pain and stress, nurturing, and sleep in preterm infants during prolonged hospitalization in the NICU. Macronutrition and micronutrition, as well as parental support, with enhancement of parental engagement both in the NICU and after discharge, may improve neurodevelopmental outcomes.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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