Neurodevelopmental Outcomes in Early Childhood

Andrea F. Duncan, MD, MSClinRes*, Melissa A. Matthews, MD

KEYWORDS

• Preterm • Neurodevelopment • Early childhood • Developmental outcomes

KEY POINTS

- Survival of preterm infants is improving, but high risk for neurodevelopmental deficits remains.
- Guidelines exist for earlier assessment and diagnosis of cerebral palsy before 6 months of age.
- High-prevalence/low severity dysfunctions are increasing.
- A longer duration of follow-up is needed.

INTRODUCTION

Technological advances in neonatal-perinatal medicine have led to a steady increase in the survival of preterm infants (**Table 1**). Indeed, survival of children at the very lowest gestations (22–24 weeks) has increased from 30% in 2000 to 2003% to 36% in 2008 to 2011.[1] Although the increase in survival is a remarkable success, children born preterm remain at high risk for brain injury and long-term neurodevelopmental deficits. As survival rates have improved over the past decades, there is an increased focus on long-term morbidity associated with preterm birth. Recently, the fact that rates of extremely preterm (<28 weeks of gestation) infant survival without neurodevelopmental impairment (NDI) have increased from 16% to 20% between the years 2000 and 2011 has been celebrated.[2] Despite this, the rate of moderate to severe NDI at 2 years of age remains exceptionally high among children at the lowest gestational ages (GAs). Of infants born at 22 weeks GA, 85% to 90% have severe NDI, with a similar outcome reported at 23 weeks GA.[3] In infants born less than 25 weeks GA, there has not been a significant improvement in neurodevelopmental outcomes in recent studies.[3,4] However, longer follow-up of these infants is needed to understand the full impact of preterm birth at the limits of viability. Additionally, even though more

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Department of Pediatrics, Division of Neonatal-Perinatal Medicine, University of Texas Health Science Center at Houston, 6431 Fannin Street, MSB 3.242, Houston, TX 77030, USA
* Corresponding author.
E-mail address: Andrea.F.Duncan@uth.tmc.edu

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Table 1
Survival of children born extremely preterm

Year	Survival Rate, %
1943–1945	0
1980–1985	10
2006–2011	65

Data from Gong A, Johnson YR, Livingston J, et al. Newborn intensive care survivors: a review and a plan for collaboration in Texas. Matern Health Neonatol Perinatol 2015;1:24.

infants at extremely low GAs are surviving, most preterm births occur in the moderate preterm (32–33 weeks' gestation) to the late preterm (34–36 weeks' gestation) range.[5,6] Although the survival rate in this cohort is greater than 99%, there is an increased risk for NDI in this group.[5,7–9]

Because of the high risk of neurodevelopmental deficits, survival without NDI at 2 years of age has become a common benchmark for success. The Eunice Kennedy Shriver National Institute of Child Health and Development Neonatal Research Network defines NDI as having one or more of the following at 2 years: moderate to severe cerebral palsy (CP), profound hearing loss requiring amplification in both ears, profound visual impairment with visual acuity less than 20/200 in both eyes, moderate to profound cognitive delay on the Bayley Scales of Infant Development 3rd edition (Bayley-III) assessment (Cognitive Composite score of <54–84), and/or a Gross Motor Function Classification System (GMFCS) level of greater than 2 on a 5-point scale.[1] A GMFCS score of 2 or greater translates functionally to a child who cannot walk or pull to stand and may or may not have head control or the ability to sit unsupported. Infant-related factors associated with survival without NDI in early childhood include female sex, higher birth weight or gestation, larger head size, and absence of neonatal morbidities and interventions.[10] Although these early benchmarks, such as NDI, are extremely important, particularly for research purposes, it must be remembered that most neurodevelopmental deficits suffered by preterm children are mild to moderate. These deficits result in a significant functional burden. In addition, preterm children are more likely to have language deficits, and far more likely to have behavioral deficits than their term-born counterparts, which may adversely impact motor, cognition, language development, and testing.[11,12] Such deficits may not be considered in research outcomes using common definitions of NDI, although they must be considered clinically. Furthermore, many developmental deficits in cognition, emotional and behavioral development, and social adaptive functioning may emerge at older ages in the absence of NDI in toddlerhood.[12,13] These "high-prevalence/low severity dysfunctions" occur in 50% to 70% of very low birth weight infants (<1500 g) and are increasing-especially in children born most premature-and include attention-deficit/hyperactivity disorder, executive function deficits, visuomotor problems, learning disabilities, and behavior problems.[12]

This demonstrates a need for longer follow-up of all infants born preterm. This article reviews neurodevelopmental outcomes for children born preterm, with a focus on early childhood.

FACTORS IMPACTING NEURODEVELOPMENTAL OUTCOMES

The factors that influence neurodevelopment in infants born preterm are multifactorial, contributing to the complexity of follow-up research and variations in reported outcomes (**Box 1**). Certain perinatal and postnatal factors confer a higher risk for long-term neurodevelopmental deficits. These include severe intraventricular hemorrhage,

Box 1
Factors affecting neurodevelopmental outcomes in preterm children

Birth weight less than 750 g or less than 25 weeks' gestation

Periventricular hemorrhage (grades III and IV) or infarction

Periventricular leukomalacia

Persistent ventricular dilation

Neonatal seizures

Chronic lung disease

Neonatal meningitis

Subnormal head circumference at discharge

Parental drug abuse

Poverty and parental deprivation

Coexisting congenital malformation

Data from Wilson-Costello DE, Payne AH. Early childhood neurodevelopmental outcomes of high-risk neonates. In: Fanaroff and Martin's neonatal-perinatal medicine: diseases of the fetus and infant. Philadelphia: Elsevier/Saunders; 2015. p. 1018–31.

periventricular leukomalacia, persistent fetal circulation, infections including meningitis and pneumonia resulting in respiratory failure, seizures, severe respiratory distress syndrome, and extremes of birth weight or GA (see **Box 1**).[14]

Preterm infants are born at a time when their brains are particularly susceptible to injury. There is significant growth and organization that occurs during the second and third trimesters. Early insults during this time may adversely affect several processes involved in brain development including neuronal migration, synaptogenesis, myelination, cytologic maturation, and cell receptor development.[10] Additionally, preterm birth and iatrogenic factors inherent to neonatal intensive care unit (NICU) care lead to increased free radical generation in the presence of decreased antioxidant capacity in preterm infants, further compounding brain injury during this vulnerable period of brain development.[15]

Factors affecting developmental outcomes begin antenatally and continue after birth. Exposure to antenatal steroids has long been shown to reduce neonatal morbidity and mortality including respiratory distress syndrome and intraventricular hemorrhage.[16] However; it is unclear if antenatal steroids have a clear benefit for neurodevelopmental outcomes. Some studies suggest an associated reduction in NDI in exposed infants born 23 to 25 weeks GA.[4,16] A significant antecedent to adverse neurodevelopmental outcomes is the presence of a perinatal infection. Intrauterine infection has been associated with a nine-fold increase in the incidence of CP in full-term infants.[12] Increased odds of NDI are also described in extremely preterm infants exposed to chorioamnionitis.[17] However, data related to the importance of intrauterine infection are unclear, particularly given the difficulty in diagnosis of intrauterine infection and the limited predictability of outcomes in preterm infants.

Postnatally, the extent of NDI may be affected in part by GA and extent of brain maturity at birth, the magnitude of the initial injury, and recurrent insults during the recovery and reorganization phase.[12] For example, birth asphyxia can lead to significant brain injury, but recurrent hypoxia compounds the damage to vulnerable neurons during the recovery phase. Additional comorbid conditions, such as bronchopulmonary

dysplasia, retinopathy of prematurity, and necrotizing enterocolitis, are associated with a several-fold increase in NDI for extremely low birth weight infants.[10,12]

The NICU environment might also impact neurodevelopmental outcomes. Although this concept remains controversial, there are studies to suggest that loud sounds and bright lights can have harmful effects on development. Conversely, decreased auditory input, particularly maternal sounds, is thought to negatively impact speech and language development.[10,18,19] It seems that auditory input is important to development, but the degree and origin of input still need to be determined.

Several other factors have been shown to play a role in adverse neurodevelopmental outcomes. Genetic factors, male gender, intrauterine growth restriction, location of birth, nutrition, high-frequency ventilation, surgery, and drug abuse are a few such factors.[10,12] Additional factors after discharge, such as maternal education, access to medical services, and socioeconomic status, also impact neurodevelopmental outcomes. These demographic factors highlight the importance of including detailed population information and a term equivalent control group in studies of early childhood outcomes in preterm children.

MOTOR OUTCOMES

Motor deficits in children born preterm are generally recognized earlier than other NDIs. Abnormal motor development, such as muscle asymmetries, hypotonia, and hypertonic extensor movements are identified before 40 weeks postmenstrual age in some infants.[8,12] In addition, preterm infants may display more extensor activity in infancy than those born term. This may be secondary to nursing postures and medical morbidities, such as chronic lung disease.[12] Children born preterm may also have transient neurologic deficits that resolve by 12 months, with rates ranging from 40% to 80%.[14] These deficits may include poor head control, generalized hypotonia or hypertonia, inability to sit at 8 months, or mild increases in extremity tone.

CP is the most common childhood physical disability, present in 0.21% of the general population in high-income countries.[20] CP is present in 9% to 20% of children born extremely preterm, and a greater proportion of preterm infants present with milder motor impairments.[10,21] The four types of CP are shown in **Table 2**. These types may develop and change during the first 2 years of life. It is of critical importance to remember that CP is often associated with significant and disabling comorbid conditions (**Table 3**).[20] Diplegia and hemiplegia are most common in preterm children, with spastic CP accounting for more than 90% of CP in preterm children.[14] Spastic CP is defined by increased tone with a velocity-dependent increase in resistance to passive

Table 2
Types and distribution of cerebral palsy

Type	Percentage
Spastic	85–91
Dyskinetic[a]	4–7
Ataxic	4–6
Hypotonic	2

[a] Includes dystonia and athetosis.

Data from Novak I, Morgan C, Adde L, et al. Early, accurate diagnosis and early intervention in cerebral palsy: advances in diagnosis and treatment. JAMA Pediatr 2017;171(9):897–907.

Table 3
Comorbid conditions associated with cerebral palsy

Condition	Percentage
Chronic pain	75
Intellectual disability	49
Epilepsy	35
Musculoskeletal problems (ie, hip displacement)	28
Behavioral disorders	26
Sleep disorders	23
Functional blindness	11
Hearing impairment	4

Data from Novak I, Morgan C, Adde L, et al. Early, accurate diagnosis and early intervention in cerebral palsy: advances in diagnosis and treatment. JAMA Pediatr 2017;171(9):897–907; and Novak I, Hines M, Goldsmith S, et al. Clinical prognostic messages from a systematic review on cerebral palsy. Pediatrics 2012;130(5):e1285–312.

movement. Assessment of passive tone using very slow stretch may therefore underestimate the degree of resistance. Hyperreflexia, protracted presence of primitive reflexes, abnormal Babinski response, abnormal posture, or abnormal movement may be present. These may be characterized in the lower extremities by equines foot position, a crouching gait, internal lower extremity rotation, and hip adduction. Upper limb findings may include arm flexion with fisting of hands, cortical thumbs, and poor coordination of finger movements.[14] Bilateral spastic CP may result in contractures.

Classically, the first 12 to 24 months of life was considered to be a "silent period" during which CP could not be accurately diagnosed. Experts now agree that the belief in a silent period is outdated, because a designation of CP or high-risk for CP may be accurately given before 6 months of corrected age.[20] Novak and colleagues[20] recently described the most predictive tools for detecting CP before and after 5 months of corrected age. Before 5 months, the most predictive tools are the Prechtl General Movements Assessment, the Hammersmith Infant Neurologic Examination (HINE), and MRI at term age with sensitivities of 98%, 90%, and 86%, respectively. However, the Prechtl Assessment has a low specificity and although the specificity of MRI is good, its sensitivity is comparatively lower.[10] After 5 months' corrected age, the most predictive tools for detecting CP are MRI and the HINE with 86% to 89% and 90% sensitivity, respectively. The HINE is used as a neurologic assessment from 2 months through 24 months.[22] The authors also note that the trajectory of HINE scores combined with abnormal MRI findings is more accurate than individual clinical assessments.[20,23] It is therefore recommended that a combination of medical history, standardized motor assessment, and neuroimaging is used when making a diagnosis of CP by 6 months corrected age.

If CP is suspected but cannot be definitively diagnosed, an interim diagnosis of high risk of CP should be given until the diagnosis may be confirmed.[20] Using the specific CP moniker is of import, because infants with CP have improved functional outcomes in response to different interventions than the interventions provided with concerns for developmental delay or autism. Early referral to CP-specific early intervention is critical to improve functional outcomes, as is continued, coordinated care including medical, neuromotor, and developmental monitoring to provide appropriate care in consideration of current diagnoses and comorbidities that may develop. A temporary diagnosis

of high-risk CP requires that the child have motor dysfunction (essential criterion) and at least one of the other two additional criteria, which include abnormal MRI (with or without serial cranial ultrasound [CUS] examinations) neuroimaging and a clinical history conferring risk for development of CP (**Table 4**).[20] The MRI findings most predictive of CP and clinical findings conferring risk are detailed in **Table 3**. CUS is also frequently used in NICUs to detect intraventricular hemorrhage, intraparenchymal hemorrhage, and ventriculomegaly among other things. Although cystic periventricular leukomalacia on CUS is a strong predictor for CP, there are infants without abnormalities on CUS that later develop neurodevelopmental deficits.[12] Additionally, it is reported that preterm individuals with normal CUS have decreased cortical gray matter volume and increased ventricle size on MRI during adulthood compared with full-term control subjects.[12] Spasticity may develop after 1 year of age, and children who

Table 4
Neuroimaging and clinical findings associated with cerebral palsy

Abnormal Neuroimaging Associated with Cerebral Palsy	
White matter injury	Cystic periventricular leukomalacia Periventricular hemorrhagic infarctions
Cortical and deep gray matter lesions	Basal ganglia or thalamic lesions Parasagittal injury Multicystic encephalomalacia Stroke
Abnormal brain development	Lissencephaly Pachygyria Cortical dysplasia Polymicrogyria Schizencephaly
Preconception	History of stillbirths or miscarriages Low socioeconomic status Assisted reproduction Abnormal genetic Copy number variations
Pregnancy	Prematurity Abnormal genetic findings Birth defects Multiple birth Male sex Maternal thyroid disease Preeclampsia Infection Intrauterine growth restriction Substance abuse
Perinatal	Acute intrapartum hypoxia-ischemia Seizures Hypoglycemia Jaundice Infection
Postnatal	Stroke Infection Surgical complications Brain injury before 24 mo

Data from Novak I, Morgan C, Adde L, et al. Early, accurate diagnosis and early intervention in cerebral palsy: advances in diagnosis and treatment. JAMA Pediatr 2017;171(9):897–907.

later develop CP may demonstrate hypotonia in very early life.[14,20] Spasticity during the first 3 months of life is a poor prognostic sign.[14] Because spasticity may develop later, the absence of spasticity early does not preclude a diagnosis of spastic CP. In addition, infants may simultaneously have multiple motor disorders, with spasticity and dystonia often occurring together. An increase in voluntary movements may be associated with an improvement or worsening of symptoms.[20]

The severity of CP is difficult to accurately assess in infants younger than 2 years, because their motor skills are developing, the presence/absence of hypertonicity may change over time, and this is a period of extremely rapid brain growth and experience/use-dependent neuronal reorganization in response the environment, including interventions and therapy.[20]

Cautious prediction of CP severity should be made using standardized tools, such as the HINE, coupled with neuroimaging data and clinical history.[20,22] At 2 years of age and after, the severity of CP may be accurately classified using the five-level GMFCS, Extended & Revised.[24] The GMFCS is an age-based, five-level system that defines motor functioning based on a child's self-initiated movement, and emphasizes sitting, walking, and general mobility. The levels are determined by the presence or absence of functional limitations including the need for mobility devices and the quality of usual movements.

Appropriate counseling is important when giving a diagnosis of CP, because parental understanding of the disease may not take the entire spectrum of disease into account. Large population studies from high-income countries indicate that two in three individuals with CP will walk, that three in four will talk, and one in two will have normal intelligence.[20]

Isolated and minor motor disorders, such as minor neuromotor dysfunction and developmental coordination disorder, which is found in approximately one-third of all preterm children, are more common than CP.[14,25] Children with developmental coordination disorder do not have neurosensory or cognitive impairments. Instead, children with developmental coordination disorder demonstrate fine and gross motor delays that cause difficulties or clumsiness with tasks, such as using pencils or silverware or performing routine motor tasks of daily living.[26] Minor neuromotor dysfunction is more subtle than CP or other, more severe motor impairments. It covers a wide range, such as difficulties with coordination, learning, and fine motor function.[25] Generally, it does not occur in isolation, and subtle deficits may compound together to cause greater academic struggles. With a prevalence of 40% in some studies, there are currently no ideal predictors of minor neuromotor dysfunction.[8,25] So-called minor motor disorders have been associated with general decrease in function and cognitive and behavioral deficits at school age.[27]

VISUAL AND HEARING OUTCOMES

Although vision and hearing deficits are the least common of the neurodevelopmental deficits found in children born preterm, they are far more common in this group than among the population at large. Medical morbidities, such as retinopathy of prematurity and brain injury, may adversely affect visual acuity. A severe visual deficit is defined as functional bilateral blindness, including visual acuity of 20/200 or worse, an inability to perceive light, or the ability to perceive light only.[4,21,28–33] Rates of severe visual impairment in preterm children range from 0% to 5%[28,30,32]; milder impairment, such as strabismus and myopia, occur in 9% to 25% of these children.[34–36] More than one-third of children born extremely low birth weight needs glasses, a rate three times higher than that seen in children born term.[12]

In general, researchers have defined severe hearing deficits as bilateral loss of functional hearing that is not corrected with amplification.[28] Few studies have included audiologic cutpoints, defining profound loss as greater than 90 dBHL.[28] In most large studies of children born extremely preterm, rates of severe or profound hearing loss are less than 2.5%.[4,21,28–30,32]

Although hearing and vision deficits are rare in children born preterm, 25% of hearing impairment and 35% of all visual impairment in the United states is accounted for by preterm birth.[28,37] In addition, most children born extremely and very low birth weight express a deficit in visuomotor function, although these are commonly diagnosed at somewhat older ages, when such tasks as copying, pegboard completion, spatial processing, visuosequential memory, and spatial organization are affected.[12,38–42] These deficits often exist even in the presence of normal IQ.[12] Of import, these problems have been noted at school age in children who had normal development at 3 years of age.[12,42] Visual function is also interrelated with other neurodevelopmental functions, because commingled deficits in visuospatial processing, spatial working memory, and attention have been found at 3 to 4 years of age in children born preterm.[12,43] Early and consistent assessment of visual and hearing function in children born preterm is therefore essential.

COGNITIVE OUTCOMES

Cognitive impairment (defined as a score >2 standard deviations below the mean on a standardized assessment) is the most common impairment seen in children born preterm between 18 and 30 months of age.[34,44] Rates of cognitive impairment vary by region and are inversely proportional to GA. In large studies of children born extremely preterm, moderate cognitive impairment has been demonstrated in 15% to 35% of children, severe impairment in 10% to 35%, and profound impairment in 10%.[21] Although motor outcomes are linked with specific areas of brain injury, early cognitive deficits are not as strongly predicted by brain region.[28]

Most large studies of neurodevelopmental outcomes in children born premature use the Bayley-III for assessment of cognitive outcomes before 3 years of age. Unfortunately, the value of early assessments of cognition in predicting cognitive functioning at school age and older is questionable.[28] In addition, defining the severity of cognitive dysfunction in early life may be difficult in preterm children, because use of standard test cutpoints without the presence of a term control group may not accurately reflect outcomes, given the propensity for lower mean scores than the normed average in this population with higher aggregation of scores in the lower range and fewer scores in the higher range.[28] The Bayley-III is also used extensively in clinical care to diagnose developmental delays and to determine subsequent qualification for early intervention services. Cognitive function is assessed by examining the following cognitive constructs: (1) sensorimotor development, (2) exploration and manipulation, (3) object relatedness, (4) concept formation, (5) memory, (6) habituation, (7) visual acuity, (8) visual preference, and (9) object permanence. These constructs are measured through assessment of age-related skills including counting, visual and tactile exploration, object assembly, puzzle board completion, matching colors, comparing masses, and representational/pretend play.

Bayley-III Cognitive Composite Scale scores range from 55 to 145 with scores of 100 $\pm$ 15 representing the mean $\pm$ 1 standard deviation.[45] Moderate cognitive dysfunction has previously been defined as a Bayley-III score of 2 to 3 standard deviations below the mean (a score of 55–70), with a severe deficit defined as a score less than 55.[28] Following the introduction of the Bayley-III, researchers found that

rates of developmental delay were greatly decreased compared with those found using the previous edition of the test.[46–48] Concerns regarding the increased scores and possible underestimation of cognitive impairment have resulted in the cutpoints for cognitive impairment being shifted when using the Bayley-III. The Eunice Kennedy Shriver National Institute for Child Health and Development Neonatal Research Network now uses Bayley-III Cognitive Composite scores between 70 and 84 to define moderate cognitive impairment, scores less than 70 to define severe impairment, and scores less than 54 to define profound impairment.[21,44] Bayley-III scores do not provide indication of particular strengths of a given child or definition of specific, subtle areas of development that may be adversely impacting performance.[28] Age at assessment is of import, with studies examining children at 18 to 22 months finding higher rates of cognitive impairment than those assessing children later.[44] In addition, in preschool years, assessment of cognition necessarily relies on language, motor, and visual function; thus, a pure cognitive assessment is difficult to obtain.[28]

LANGUAGE OUTCOMES

Language deficits are common in premature infants in early childhood and may include abnormalities in receptive language, expressive language, and articulation.[49–54] As with other NDIs in preterm children, language deficiencies are often interconnected with other deficits including CP, hearing loss, behavioral abnormalities, and cognitive deficits.[49,55] In addition, various biologic and environmental factors may adversely influence language outcomes in preterm children (**Box 2**).[49,56] Auditory exposure to language is also critical for language development.[57] Development of the auditory cortex and speech development require an infant to be regularly exposed to speech.[57] Early language function is essential to social interaction and later school achievement.

Language is categorized in different domains. In early language development, expressive language (production) and receptive language (comprehension) are generally considered separately, and receptive language development precedes language production.[50] Phonologic awareness (understanding of speech sounds) may also be considered.[50] Phonologic awareness is of particular import during early language

Box 2
Factors influencing early language development in preterm children

- Gestational age
- Illness severity
- Increased number of neonatal morbidities
- Duration of hospitalization
- Hearing status
- Gender
- Age at assessment
- Socioeconomic risk factors
- Environment
- Feeding difficulties

Data from Vohr B. Speech and language outcomes of very preterm infants. Semin Fetal Neonatal Med 2014;19(2):78–83.

development but, to our knowledge, has not been largely studied in preterm children in early childhood to date.[50]

Numerous studies have consistently demonstrated that children born preterm have significantly lower expressive language ability than their term-born peers, although effect sizes seen are often varied. The heterogenous ages at assessment likely contributed to these findings, along with the numerous assessment tools used.[50] Language differences found remain after adjustment for disability and socioeconomic status.[53,58] Receptive language studies in preterm children are rare and largely performed at school age, rather than early childhood.[50,59,60]

BEHAVIORAL OUTCOMES

Children born preterm are up to four times more likely to have behavioral problems than children born at term.[61] Normal behavioral development is crucial to socioemotional functioning and has strong influences on the development of motor function, cognition, and language.[55] Most studies of behavioral outcomes in preterm children report on children at school age or adolescence; however, lower rates of social responsiveness have been demonstrated in preterm infants in early infancy.[62] The few studies of behavioral outcomes in preterm children during infancy and preschool age have demonstrated poor social/interactive skills, externalizing and internalizing disorders, emotional dysregulation, aggression, reduced attention, and hyperactivity.[63,64] There is also evidence that behavioral deficits identified in toddler years remain stable from early childhood through school age; and lower social competence in the preschool years is associated with more externalizing and internalizing behavior problems at 10 to 14 years of age.[65,66] However; longitudinal studies of behavior in preterm children are rare. In the last decade, researchers have put forth a "preterm behavioral phenotype" consisting of inattention, anxiety, and social difficulties.[67]

Although the exact cause of the behavioral abnormalities noted in premature infants is unknown, medical complications, home environment and socioeconomic factors, and perinatal brain injury have been implicated.[68] In a large recent study of children born less than 27 weeks' gestation at 18 to 22 months, Peralta-Carcelen and colleagues[55] demonstrated that 35% of children had behavioral problems, and 26% had deficits in socioemotional competence measured using the Brief Infant and Toddler Social and Emotional Assessment (BITSEA). Male sex, public insurance, maternal education of less high school, and lower maternal age were associated with behavioral problems. Socioemotional competence deficits were associated with lower birth weight, public insurance, mothers with less than a high school education, and abnormal neuromotor examination. In addition, language and cognitive scores on the Bayley-III significantly mediated the relationships between risk factors and behavioral and competence scores.

CUS and MRI at term equivalent have been associated with cognitive, psychomotor, and neurosensory delays at 18 to 24 months of age; however, there is a paucity of data describing early behavioral correlates to imaging findings.[69,70] Four-year-old children born extremely premature are more likely to have severe executive function deficits if they had global moderate-to-severe white matter injury signal abnormalities on standard T1- and T2-weighted MRI performed at term GA.[71] Executive function refers largely to cognitive processes, but behavioral abilities, such as self-regulation and inhibition, are vital to executive functioning.[72]

Abnormalities in specific brain regions may also have a role in behavioral outcomes. Cerebellar injury has been associated with developmental outcomes in premature infants. Corpus callosum length has been independently associated with poorer

inhibition and emotional control at 4 years, and corpus callosum thickness has been correlated with white matter volume.[73,74]

Behavioral function may be assessed in early childhood using such tools as the BITSEA and the Child Behavior Checklist.[75,76] The BITSEA is a parent-completed rating scale for children 12 months, 0 days to 35 months, 30 days. It includes 42 items and yields standardized scores for the Problem and Competence Scales based on age and gender. The Problem Scale assesses for externalizing problems (disruptive or aggressive behaviors), internalizing problems (ie, anxiety, withdrawal), dysregulation, and maladaptive and atypical behaviors. Higher Problem Scale scores indicate more difficulties in these areas. The Competence Scale assesses the social emotional competencies that emerge at this age, such as symbolic and imitative play and cooperation. Lower Competence Scale scores indicate lower social emotional competencies. Total standardized scores and Positive Screen scores were assessed for each of the scales. A Competence Scale score of less than or equal to 13 or less than or equal to 15 (for boys and girls, respectively) and a Problem Scale greater than or equal to 15 indicates positive screens for children aged 18 to 23 months.

Behavioral and socioemotional deficits may impede learning, thus early assessment of behavioral functioning is critical so that appropriate intervention may be provided. Trials of parenting interventions in early childhood have demonstrated improvement in behavioral problems and improved behavioral competence among typically developing infants and children and preterm children.[77,78]

THE MODERATE AND LATE PRETERM INFANT

The increased rates of prematurity recently seen have been largely secondary to increased rates of moderate preterm (32–33 weeks of gestation) and late preterm (34–36 weeks of gestation) birth, because these children account for 84% of all preterm births.[6,79,80] Although the literature is still emerging in this area, studies demonstrate that children born moderate and late preterm are at increased risk for neurodevelopmental deficits. In a study of 1130 infants born 32 to 36 weeks of gestation, Johnson and colleagues[80] demonstrated children born moderate to late preterm to be at double the risk for neurodevelopmental disability at 2 years of age, with most deficits observed in the cognitive domain of function. Male sex, low socioeconomic status, and maternal preeclampsia were independent predictors of low cognitive scores. Studies of late preterm infants have demonstrated rates of CP 10 times greater than that of the general population.[9,81] Deficits in language and visuospatial ability have also been demonstrated.[7,9] These findings highlight the need to follow children born moderate and late preterm for neurodevelopmental deficits.

SUMMARY

Preterm children remain at high risk for neurodevelopmental deficits in early childhood, with the prevalence of milder deficits increasing. In addition, new guidelines for early assessment and diagnosis of CP are of particular import to these children. Currently, no standardization exists for follow-up of children born preterm, and practices vary among centers.[82] Most research studies to date have focused on outcomes before age 3, with many follow-up sites following children to that age or before. Access to appropriate, long-term follow-up care and resources for preterm infants after discharge from the NICU plays a critical role in improving and maintaining function over time, because early assessment and intervention improves neurodevelopmental outcomes.[83,84] These findings point not only to a need for standardization of follow-up, but to the import of longer follow-up, because children may have normal assessments

during infancy, with deficits emerging over time as the child is challenged with more complex tasks. A normal early assessment does not exclude the possibility of impairments becoming unmasked at a later age, thus emphasizing the need for longer term, comprehensive follow-up of preterm infants.

Best Practices

What is the current practice?

Children born preterm are at increased risk for developmental delay in early childhood in motor, cognitive, language, and behavioral domains.

Best practice/guideline/care path objectives

Comprehensive developmental assessments are recommended for children born preterm.

Summary statement

Preterm children remain at high risk for neurodevelopmental deficits in early childhood, with the prevalence of milder deficits increasing. There is a need for standardized, longer term follow-up, because deficits may emerge over time.

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