An overview of risk factors for poor neurodevelopmental outcome associated with prematurity

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Background: **Preterm birth is a major cause of neonatal mortality and morbidity. While advances in medical care have improved the survival of preterm infants, neurodevelopmental problems persist in this population. This article aims to review factors associated with their neurodevelopmental outcomes.**

Data sources: **English language studies of neurodevelopmental outcomes in preterm infants were retrieved from PubMed. A total of 100 related publications were included.**

Results: **Early gestational age and birth weight are the most significant predictors of poor long-term neurological outcome. Structural changes of the brain, infection, male gender and neonatal intensive care unit course are also important factors affecting eventual outcome. Other complex biological and socio-economic factors, which extend from prenatal through postnatal periods, up through and including adulthood, also affect the trajectory of brain development in preterm infants.**

Conclusions: **Neurodevelopmental problems continue to affect the preterm population. There is a critical need for collaboration among geneticists, obstetricians, pediatricians, and neuroimaging and rehabilitation experts to determine early predictive factors and neuroprotective therapies to properly treat or prevent poor neurodevelopmental outcomes in these infants.**

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Review article

Introduction

Preterm birth accounts for 9.6% of all live births and is a major cause of neonatal mortality and morbidity worldwide. There is a trend toward increased morbidity secondary to increased survival of preterm infants.[1,2] Complications arising from preterm birth are also the leading cause of neonatal and infant mortality worldwide.[3] Given improved survival, characterizing the long-term neurodevelopmental risks and prognosis after preterm birth has been particularly important. There is no decrease in the rate of major neurodevelopmental disability, including cerebral palsy (CP) and severe intellectual disability.[4] In addition, more subtle motor and cognitive dysfunction resulting in regulatory, attention, social and adaptive problems has emerged.[5] This applies to premature newborns with significant intraventricular hemorrhage (IVH) or white matter injury. Those without severe brain injury are at risk for cognitive dysfunction and may still require more support than their full-term peers.

These disabilities reduce health-related quality of life and result in considerable health care costs.[6,7] In preterm infants, costs per infant hospitalization are highest for extremely preterm (EPT) infants.[8] Although the costs per case decrease exponentially with increasing gestational age, total neonatal costs are not necessarily less for other gestational age groups, because of increasing case numbers with advancing gestational age.[9] Furthermore, preterm infants incur higher early intervention costs, compared with their full-term counterparts.[10] Thus, preterm infants in the United States account for half of all infant hospitalization costs and one quarter of all pediatrics costs.[8]

Preterm birth is a significant obstacle to the normal neurodevelopmental trajectory from fetus to adult. Although preterm birth is associated with various

neurodevelopmental problems, a considerable proportion of these infants can escape major impairments, even in the most vulnerable subgroups.[11] This variability in neurodevelopmental outcome likely reflects interactions between biological and social factors associated with preterm birth. Interactions between prenatal, postpartum, and later factors all play major roles in the development of the preterm infants. Therefore, we summarize studies related to neurodevelopmental outcomes in preterm infants to probe the important factors that influence later disability and dysfunction.

Effects of gestational age and birth weight on preterm neurodevelopment

Preterm infants are generally divided into three different groups based on gestational age: EPT (<26 weeks), very preterm (VPT, 26-33 weeks), and late preterm (LPT, 34-36 weeks).[12] In many studies of neurodevelopmental outcome, birth weight is also used. Birth weight categorizations include extremely low birth weight (ELBW, <1000 g), very low birth weight (VLBW, <1500 g), and low birth weight (LBW, <2500 g). As gestational age and birth weight increase, all grades of disability decrease.[13-15]

EPT infants represent a rapidly increasing subpopulation that is at the highest risk for poor outcome.[16] Neurodevelopmental outcomes of EPT infants are very heterogeneous among different centers. The prevalence of neurodevelopmental disability ranges from 20% to 59%.[17-26] Two recent systematic reviews calculated that the mean prevalence of disability for EPT infants is 36% (range: 12.4%-57.5%).[27,28] This variation may be due to different criteria for identifying disability, or differences in neonatal intensive care unit (NICU) practice and postnatal care. The infants born at the gestation of 23 or 24 weeks have a 1.8-fold increased risk for impairment compared with those born at the gestation of 25 weeks.[24] In infants with a birth weight <501 g, 56% survived to school age while 74% of the survivors showed abnormal neurological function.[29]

VPT and VLBW infants comprised 1%-2% of all live births.[30] The prognosis is better for VPT infants than for EPT infants.[31] Large population-based studies report that the prevalence of major developmental disability in VPT is 13%,[32] with a severe disability rate as high as 5%.[13] When considering mildly abnormal IQ testing, behavior questionnaires, or motor and neurologic testing, 50% of VPT children demonstrate more than one abnormality at the corrected age of 5 years.[33] Because intellectual, motor and behavioral function is often compromised, fewer VLBW patients are subjected to post-high school studies.[17,34]

LPT infants, who represent the majority of preterm births, generally require less medical support to survive, and their risk for long-term complications is often underappreciated. Evidence suggests that LPT infants are also at increased risk of adverse developmental outcomes and academic difficulties in comparison to full-term infants.[35] LPT children are more likely (three times) to be diagnosed with CP, and their risk for mental retardation is marginally higher than that in full-term children [odds ratio (OR), 1.25].[36] Since there are paucity and heterogeneity of the existing data in LPT infants, the prevalence of major developmental disabilities is not clear in this population.[37]

The impact of low birth weight and early gestational age is the greatest during the early years.[38,39] As age increases, the influence of birth weight and gestational age declines, but they do continue to extend into adolescence and adulthood.[6,40,41] Birth weight and gestational age are positively correlated with internalizing and externalizing behavioral problems,[39] including an increased risk for autism.[42-44] In addition, the relative risk for hospitalization for epilepsy is markedly increased in those born at earlier gestational ages, even in late preterm infants. OR for hospitalization for epilepsy is 1.76 for those born at 35-36 weeks, 1.98 for those born at 32-34 weeks, and 4.98 for those born at 23-31 weeks, relative to those born full-term.[45]

General factors

Injuries/structural changes in the brain

Structural changes in the brain may often be the source of neurological dysfunction in preterm infants. A variety of factors can lead to gross or fine structural changes in the vulnerable preterm brain, and subsequently affect neural function. Functional outcomes are closely related to the location and severity of injury, and cerebral volume is an independent predictor of neurodevelopmental outcome. For example, smaller brain volumes, ventriculomegaly, and decreased callosal projections and altered fiber tract organization have been associated with poor neurodevelopmental outcome.[46,47] Reduced gray matter and white matter volumes in prematurity are also correlated with cognitive outcomes at 9 years of age.[48]

Parenchymal lesions identified by MRI are a reliable predictor of outcome with a relatively high sensitivity and specificity.[49] In addition to motor impairment, cerebral cortical damage is often associated with three other types of impairment: epileptic, cognitive, and psychological.[50] White matter injury may explain impaired cognition, neurosensory

and motor function, as well as the development of CP in premature infants.[51,52] Morphological changes in the brainstem can also predict neurosensory disability to some extent,[53] and reduced cerebellar diameter at term equivalent age is associated with abnormal general movements.[54] Cerebellar hemorrhagic injury in preterm infants is also associated with a higher prevalence of long-term neurodevelopmental disability. Neurological abnormalities are present in 66% of infants with isolated cerebellar hemorrhagic injury, including cognitive, learning, and behavioral dysfunction.[55] Other cerebral abnormalities, especially cystic periventricular leukomalacia (PVL), are associated with CP at school age. Outcomes after periventricular hemorrhagic infarction are better than what are thought previously. In survivors, only the most extensive form of periventricular hemorrhagic infarction is associated with the development of CP.[56] High-grade IVH and/or PVL are significant risk factors (OR=13.3) for developing minor or major impairments at school age.[57] Cerebral ventricular dilatation is an additional risk factor for poor intelligence and abnormal fine motor function.[58]

Infection

Infectious processes and their accompanying systemic inflammatory response dramatically increase the risk of long-term neurologic sequelae. Many causes of systemic inflammation have been shown to be detrimental. For example, during the neonatal period, necrotizing enterocolitis, a common infectious disease involving the gastrointestinal system in preterm infants, may initiate systemic inflammation that can potentially affect the brain.[59,60] It has been reported that children with necrotizing enterocolitis are not at increased risk of developmental problems.[61,62] However, necrotizing enterocolitis requiring surgical intervention is associated with significant growth delay and adverse neurodevelopmental outcomes at the corrected age of 18 to 22 months.[62]

It has also been demonstrated that primary central nervous system infections can lead to brain injury. Combined with IVH or PVL, they may further contribute to adverse neurodevelopmental outcome, including the development of CP, developmental delay of mental processes, psychomotor problems and visual impairment.[63,64]

Sex

Sex-based differences in brain maturation and neurobehavioral function are incompletely understood. Females are known to be neuro-protected and secondary to vulnerability of males to certain types of white matter injury.[16] In EPT infants, overall impairment is more common in males than in females (OR=1.8).[24,65] Male sex appears to be an independent predictor of lower movement assessment scores, CP and autism spectrum disorders.[31,42,66] Male sex is a predictor of deafness (OR=2.79),[67] and males are twice as likely to have language deficits.[68] In LPT infants, male sex is associated with lower MDI scores than females at 18 months.[69] However, females do show a trend toward suffering from more emotional and behavioral problems, and ex-VLBW adolescent females have more emotional and externalizing problems than males.[70]

NICU care

Improvements in NICU care, such as surfactant administration and methods of ventilatory support, have dramatically decreased preterm mortality. It is possible that medical management in the NICU has also significantly affected the neurodevelopmental outcome of preterm infants.

Medications used in the NICU may influence the development of the nervous system of infants. Postnatal corticosteroid administration is associated with abnormal neurologic outcomes, including CP and low Bayley PDI and MDI scores.[19,23,57] The effect of postnatal steroids on CP may depend on three factors: the risk of chronic lung disease, steroid administration time and cumulative doses.[71] For babies with a high risk of chronic lung disease, steroid treatment may reduce the risk of CP. On the other hand, for babies with a low risk of chronic lung disease, steroid treatment increases the risk of CP.[72] CP rates are also increased by early (<8 days), but not delayed (>8 days) initiation of steroid treatment.[73] The CP risk also appears to be affected by the cumulative dose given. For example, in the second week of life, higher cumulative doses have a lower risk of combined CP and mortality than earlier treatment;[74] whereas lower cumulative doses may have better neurological outcomes after the third week of life.[75] Finally, mechanical ventilation also contributes to long-term deficits.[76] Infants who receive mechanical ventilation >14 days have a more than two-fold chance of neurodevelopmental impairment at school age.[57]

Other factors

Prenatal period

In the prenatal period, growth restriction or small for gestational age status represents an independent risk factor in preterm children, with associated cognitive and behavioral deficits.[77] In addition, chorioamnionitis, preterm premature rupture of membranes and maternal infection are independent predictors of CP.[66,78,79]

Twin gestation in ELBW infants is also associated with an increased risk of death or neurodevelopmental impairment at the corrected age of 18-22 months compared with singletons, with both first- and second-born twins being at increased risk.[80]

Neonatal period

Disease

Being in an extra-uterine environment during the 24-40 weeks gestational period has a profound and long-lasting impact on brain development.[81] While birth asphyxia, birth trauma and other adverse events during labor contribute significantly to the future development of CP,[82] systemic disturbances during early neonatal care of premature infants have significant effects on cognitive and behavioral function at school age and adolescence. These disturbances include the development of chronic lung disease, necrotizing enterocolitis, apnea and bradycardia, hypothyroxinemia, hyperbilirubinemia and nutritional deficiencies.[83-85] Recurrent hypoxic and bradycardic spells due to apnea may lead to brain injury. For example, the increase of days that apnea is recorded during hospitalization is associated with a worse Bayley outcome at age of 3 years.[86]

NICU environment

The stressful environment of a neonatal intensive care unit, including high noise levels, frequent bright light, and interference with maternal-infant interaction may contribute to negative outcomes.[85] Acute painful events and prolonged stress may also lead to early neurologic injury and alteration of psychokinetic development in addition to long-term neurodevelopment.[87]

The change of this environment may minimize its negative effects. Developmental care including interventions to minimize the stress of NICU is important. These interventions may include elements such as control of external stimuli (vestibular, auditory, visual and tactile), clustering of nursery care activities, and positioning of the preterm infant. Developmental care can improve head circumference measurements, decrease the incidence of IVH and ventricular dilation, and enhance neurobehavioral and neurophysiological functioning.[88,89]

Nutrition

Nutrition and physical development after birth also plays an important role. Receiving total or partial parenteral nutrition ≥6 weeks is a significant risk factor (OR=2.5) for the development of impairment at school age.[19] Growth velocity during NICU hospitalization of an ELBW infant exerts a significant and possibly independent effect on neurodevelopmental and growth outcomes at the corrected age of 18 to 22 months.[90] The beneficial effects of ingestion of breast milk in NICU may also persist on cognition and behavioral function at the corrected age of 30 months.[91,92]

Infancy

Social and environmental factors

After the neonatal period, the development of the immature brain depends not only on biological factors but also on the contribution of many social and environmental interactions.[39] These factors include overall socioeconomic status, including the home environment and family capital (parental education, parental mental health, maternal age, race, maternal substance use, parental/caregiver attitudes, marital status and one- or two-parent families), which contribute to the neurodevelopmental outcomes of VLBW and ELBW survivors.[5,16,33,85,93] In particular, family and community support may play a crucial role in this process.[5] Low socioeconomic status can be conceptualized as a marker for a larger collection of adverse environmental factors, such as limited parental education and minimal fiscal resources, which may also contribute to behavioral problems.[94] The optimal environment can compensate, to some degree, for intelligence delay secondary to biological changes. Preterm infants born of highly educated parents have higher IQs than those born of less well-educated parents, probably reflecting a combination of educational and environmental influences. Maternal age is also associated with intelligence, as infants born to mothers aged 25-30 years have a higher IQ than those in other age groups.[95] This is closely intertwined with socioeconomic status, and may also include nursing experiences and physical condition as important factors.

The immature behavioral organization of preterm infants can present a challenge to parent-child interaction. Life-threatening events in the perinatal period might also induce overprotective parental behavior, leading to inadequate socio-emotional behavioral adjustment in the child.[96] In addition, negative parental behavior, exposure to violence and high levels of family adversity are associated with the emergence of problems in early childhood and predict their persistence at school age.[97]

Early intervention

Early developmental intervention has been utilized to improve the functional outcome of preterm survivors. Early intervention includes physical therapy, occupational therapy, neurodevelopmental therapy, parent-infant relationship enhancement,

Table. Risk factors for poor neurodevelopmental outcomes in preterm infants

	Risk factors
Gestational age/ birth weight	Low gestational age
	Low birth weight
General factors	Injury/structural changes in the brain
	Infection
	Sex
	Neonatal intensive care unit practice
Prenatal period	Growth restriction
	Small for gestational age
	Chorioamnionitis
	Preterm premature rupture of membranes
	Twin gestation
Neonatal period	Birth asphyxia; birth defects; adverse labor events
	Chronic lung disease; necrotizing enterocolitis
	Apnea and bradycardia
	Hypothyroxinemia; hyperbilirubinemia; seizures
	High noise levels; constant bright light
	Interference with maternal-infant interaction
	Nutritional deficiencies; slow growth velocity
	Small head circumference; lack of breast milk
	Lack of developmental care
Infancy through adulthood	Lack of developmental interventions
	Poor home environment: distressed neighborhoods
	Poor parental capital: divorced parents, low parental education, poor parental mental health, inappropriate maternal age, maternal substance use, bad parental/ agecaregiver attitudes, low socioeconomic status

infant stimulation, infant developmental care, and early educational intervention.[98] Although early developmental interventions have a positive influence on cognitive outcomes in the short- to medium-term, they have not shown any benefit for cognitive outcomes at school age. Furthermore, early interventions have less effect on motor outcomes in preterm infants, suggesting that the benefits of developmental intervention are restricted to relatively short-term gains in cognitive function (Table).[98,99]

Conclusion

Many aspects of brain development including motor function, intelligence, behavior, emotion and language can be displaced from their normal trajectory because of premature delivery. However, even in ex-ELBW and VLBW adults with neurologic impairment can lead to productive and healthy lives, and self-report either no difference or only a small reduction in quality of life.[100]

Neurodevelopmental disabilities in preterm infants result from a complex interaction of biological and socioeconomic factors. These factors play roles in prenatal, perinatal, and postpartum periods, extending from the neonatal period through adulthood. It is worth noting that most risk factors have been identified from either cohort or case-control studies, and possible confounders may bias the results or conclusions because of lack of evidence from well designed randomized controlled trials. The results of some studies may not accurately reflect outcomes of recent practice, because of changes of clinical guidelines. Consequently, there is a critical need for collaboration among specialists from a number of different disciplines including genetics, epidemiology, obstetrics/gynecology, pediatrics, neuroimaging and rehabilitation specialists to predict, prevent and improve the adverse neurodevelopmental outcomes that occur in some preterm infants.

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