

Neurodevelopmental Outcome of Preterm Infants at Childhood: Cognition and Language

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With the recent advancement of antenatal intensive care and facilities for neonatal intensive care, the survival rate of preterm infants including extremely low birth weight infants has been significantly improved. Despite without structural disruption of the brain, the altered brain development might drive preterm infants to be prone to every neurodevelopmental disorder including cerebral palsy, cognitive impairment, language delays, behavioral disorders, and executive function deficit in school age. Many studies reported that preterm children had long-term inferiority among peers in the area of cognitive and academic performance. Follow-up studies of neurodevelopmental outcome in children born prematurely deserve clinical attention, not only to decrease morbidity related prematurity but also to achieve high quality of life of preterm infants. Recent studies have been focused on the cognitive and language outcome of preterm infants. The aim of this article was to clarify the impact and consequences of preterm birth and/or very low birthweight without major disabilities on brain development throughout childhood, focusing on cognition and language function.

Key Words: Neurodevelopmental Disorders; Infant, Newborn; Infant, Premature; Cognition; Executive Function

INTRODUCTION

The preterm/very low birthweight (VLBW) are at particularly high risk of neurodevelopmental impairment. The prevalence of cerebral palsy has decreased over the previous era. Recent advances in perinatal care decreased rates of major neurodevelopmental disability at preschool age. Recent data suggests that 85% of VLBW infants survive in the 2014 Korean Neonatal Network. Until recently, most of the studies reported in Korea were mainly focused on major disabilities, such as cerebral palsy, vision and hearing disabilities. However, as a result of long term observation of very small infants, it is now evident that a variety of different complications may commonly occur in preterm infants without major disabilities as follows: learning disability, borderline intelligence quotient (IQ), attention deficit/hyperactivity disorder, visuomotor integration disorder, executive dysfunction, and behavioral disorder. A follow-up study for at least 6 years revealed that 42% has minor

disabilities including light mental retardation, language disorder, hearing abnormality, and ADHD [1]. Ultimate goals of thorough care of preterm infants include not only to decrease the death rate but also to increase the quality of life for survived, high risk infants. This review will discuss about the existing data of neurodevelopmental outcome in preterm infants, to improve understanding of the negative consequences of very preterm/VLBW birth on brain development throughout childhood.

STRUCTURAL BRAIN PROBLEMS IN PRETERM INFANTS

Alterations in the normal maturation of the brain impacts the myelination process in very preterm/VLBW children. There is strong evidence that brain volume reduction in white and grey matter is associated with decreased general cognitive functioning throughout childhood and adolescence [2,3]. In particular, recent

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research such as functional MRI and diffusion tensor imaging showed that volumetric loss of specific brain regions in sensorimotor cortex, cerebellum, corpus callosum and hippocampus was evident in preterm/VLBW infants, leading to underlying function deficits such as lower cognitive scores and behavioral disorders during brain development [4].

The disruption of the normal maturation process during brain development as well as brain injury of the immature brain seems to be associated with negative consequences. Despite ongoing studies on the underlying mechanisms causing differences in neurodevelopment between very preterm/VLBW children and term-born peers, recent literature indicates that pre-oligodendrocytes, axons, and subplate neurons might be negatively influenced by inflammation and hypoxic/ischemic events.

COGNITIVE OUTCOME

The neurocognitive evaluation preterm/VLBW child demands a long term follow-up period of at least 6 years for reliable developmental prognosis [1]. Diagnosis of cerebral palsy could be found at the age of 2 years in the longitudinal evaluation with correct diagnosis, whereas cognitive impairment was hardly detected [1]. Population-based prospective cohort in Sweden showed 73% had mild or no disability in extremely preterm infants born before 27 weeks of gestation at 2.5 years after receiving active perinatal care [5]. However, the longer the period of tracking, the higher the ratio of correct prediction, resulting in 59% and 70% at the age of 12 months and 4 years, respectively [1]. In fact, there was a trend for worsening outcome over follow-up period, suggesting shorter period of observation in neurodevelopmental outcome results in decreased reliability. Since the high percentage of isolated cognitive deficiencies without motor deficit is undetected in extremely low birth weight (ELBW) infants, active interest and further development of solutions for these problems are necessary.

Mean IQs of VLBW was lower than normal compared to full term infants by 3-9 points with the decrease predicted to be approximately 1.7 IQ points per week [6]. In ELBW infants, the <750 g birth weight group has lower IQ compared with that of normal full term infants at middle school age, with IQ <70 lower by 9.5 times [7]. Overall, lower average score of IQ appears to be an important predictor of poor condition in academic accomplishment and educational difficulties [6,8]. In a big follow-up study by the EPIPAGE cohort of children born before 33 weeks, gestation, iso-

lated cognitive deficiency, even in the case without significant cerebral damage, remained high with 23% at 8 years [9]. They demonstrated that VLBW infants had poor cognitive and language performance in comparison with term infants. These results should encourage longitudinal follow-up for these problems in very preterm children, including the less immature and those without cognitive impairment. The EPICure cohort is the largest population-based study investigating the outcome of children born <26 weeks, gestation. IQ scores for the EPICure children born at 23-25 weeks decreased linearly by 2.5 points weakly in gestational age at 6 years of age [10].

LANGUAGE SKILLS

Sansavini et al. suggested that preterm infants have different developmental trajectories with a slower rate in gestures/actions and word production, increasing divergence from 12 to 24 months, compared to full-term infants in a systematic longitudinal analysis [11]. Recent findings highlighted in preterm/VLBW infants has been an important determinant of language development in infancy, and also in later language outcome at school age, even in the absence of major disabilities associated with prematurity [12,13]. While primary speech and language disorders are found in 11% of average preschool children, prevalence increases to 24-34% among preterm infants [14-16]. While a motor condition can be easily recognized at early childhood, cognitive and language deficits don't surface until early childhood, generally emerge later in middle childhood [17]. Language development at age three or four can facilitate later reading skills and academic achievement as well as social competence [18].

More importantly, when language functions are divided into simple verbal process and complex language function, including the integration with multiple language component and abstract concept, preterm infants demonstrated more difficulty in more complex language function, compared with term-born children [19]. Consequently, preterm-born children continued to lag behind term-born children during transition to young adulthood from 3 to 12 years of age, while term-born children who are "late talkers" were likely to catch up with their peers until the age of three [20].

However, it is still unclear that to what extent variations in language acquisition of preterm infants are individually affected by cognitive problems and environmental factors as well as genetics.

Some children with familial background of language delay catch up with peers during the preschool years, moreover these children do not have any other deficits such as cognitive, receptive language, or socio-emotional. The inter-individual variability in development of language should be considered according to cognitive function and social economic status, when preterm/VLBW infants' language is evaluated. It has been suggested that language impairment could be a result of general cognitive difficulties complicating attention and working memory [21].

EXECUTIVE FUNCTION

Executive function refers to integrated cognitive processes related to the functions of prefrontal cortex that control goal-oriented and purposeful behavior [22]. Three cores of executive functions are impulse control, working memory and cognitive flexibility. Ni et al. showed that VLBW infants developed early abnormal executive function at 6 years of age with five tasks, including the Comprehensive Nonverbal Attention Test Battery, Wisconsin Card Sorting, Tower of London, Span Subtest and Knox's Cube Test Digit [17]. These executive functions have been strongly correlated with academic achievement and behavioral functioning [23]. Another study by Aarnoudse-Moens et al. [22] reported that preterm/VLBW children at early school age have deficits in executive function even after controlling IQ, compared with full-term controls. Since executive function is crucial in social and academic achievement, early detection and timely intervention of executive function may improve substantial impairment at long-term inferiority in comparison with term infants.

BEHAVIORAL OUTCOMES

There is little consensus regarding behavioral problems that are strongly associated with the presence of cognitive impairment, but most studies show an increased psychiatric risk of inattention-hyperactivity, autism and social problems even after adjusting for cognitive function [23-25]. Lower gestational age is an independent risk factor of autism spectrum disorders, with prevalence by 3 fold in infants < 27 weeks compared with term infants [26]. Hack et al. found that 4% of extremely low birth weight infants had positive screening prevalence for autism spectrum disorder at 8 years of age [27]. Recent research addressed the bullying issue of preterm children at school age in the German Bavarian Longitudinal Study

(preterm/VLBW infants) and the EPICure study (ELBW infants) [28]. In regression analysis, preterm-born children were more vulnerable to being bullied by peers, after controlling for sex, socioeconomic status, disability, and preexisting emotional problems. This emerging social problem proposes that further study should be needed to determine whether abnormal brain development related to white matter pathology may explain why autistic spectrum disorder form multifactorial origins, causing behavioral problems in preterm/VLBW infants.

CONCLUSION

In summary, preterm birth may be associated with early lags in language function and later poor competence that contribute to learning-related problems at school-age, even in absence of major disabilities. Further, it is possible that complex language impairment only surfaces at school age, related to learning disabilities. Early detection of cognitive problems among very preterm children should be encouraged to deal with these difficulties as early as possible. It is crucial to provide thorough follow-up of IQ and language skills for preterm children in order to evaluate the need for intervention. Early evaluation can help to recognize children with language delay who will benefit from early intervention.

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