 ORIGINAL ARTICLES

Impaired Language Abilities and White Matter Abnormalities in Children Born Very Preterm and/or Very Low Birth Weight

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Objectives To investigate language abilities in children born very preterm (VPT; <32 weeks' gestational age) or very low birth weight (VLBW; <1500 g) at 7 years of age and compare their performances with children born at term, and to determine whether group differences could be explained by cerebral white matter abnormality on neonatal magnetic resonance imaging.

Study design A cohort of 198 children born <30 weeks' gestational age and/or <1250 g, and 70 term controls were examined. White matter abnormalities were rated quantitatively on brain magnetic resonance imaging at term-equivalent age. Language was assessed at age 7 years using standardized language tests. Differences between groups were tested in the 5 language subdomains of phonological awareness, semantics, grammar, discourse, and pragmatics. A mediation effect was tested between birth group, white matter abnormality, and language subdomains.

Results The VPT/VLBW group performed significantly worse than controls on all language subdomains (all $P < .001$). White matter abnormality mediated the effect of group differences on phonological awareness, and partly mediated this effect for semantics, grammar, and discourse. White matter abnormality was not significantly associated with pragmatics ($P = .13$).

Conclusions Language is an important area of concern in children born VPT/VLBW. Neonatal white matter abnormality is an important predictor of outcome; however, different language abilities are differentially associated with neonatal white matter abnormality. *(J Pediatr 2013;162:719-24)*.

Children born very preterm (VPT; <32 weeks' gestational age [GA]) or very low birth weight (VLBW; <1500 g) are at an increased risk for a number of cognitive impairments in childhood.[1-3] Language has a crucial role in communication, academic achievement, and social function,[4,5] and 2 recent meta-analyses have demonstrated that language ability is reduced in children born VPT/VLBW compared with peers born at term.[6,7] In the meta-analysis by our group,[7] language was divided into subdomains that included semantics (the comprehension and expression of word meanings) and grammar (the form or structure of language). In these subdomains, school-aged children born VPT/VLBW were shown to perform 0.40-0.59 SD below term controls. However, this meta-analysis revealed that no studies meeting inclusion criteria had been published for other subdomains of language, namely phonological awareness (the sounds of language), discourse (narrative in text or conversation), or pragmatics (socially and contextually appropriate use of language). In a limited number of additional studies, phonological awareness was reduced in children born preterm and/or low birth weight when compared with term children.[8,9] It is, therefore, vital that language outcomes are examined comprehensively in modern cohorts of children born VPT/VLBW, using high quality methodology including the recruitment of unselected samples and a term control group.

The predominant brain pathology of prematurity is white matter abnormality, including cystic or punctate lesions, signal changes on magnetic resonance imaging (MRI), enlarged ventricles, or loss of white matter volume.[10-13] A degree of white matter abnormality has been estimated to affect as many as 72% of children born VPT/VLBW.[14] It has been proposed that this white matter pathology is the neural substrate for the cognitive difficulties seen in this population.[12,15,16] The degree of white matter abnormality may partly account for the reduction in language ability in children born VPT/VLBW.

We hypothesized that children born VPT/VLBW would perform worse than term children, across the 5 language subdomains of phonological awareness, semantics, grammar, discourse, and pragmatics. It was also predicted that white matter abnormality would partly mediate the relationship between birth group (VPT/VLBW or term) and language.

CELF-4	*Clinical Evaluation of Language Fundamentals-Fourth Edition*
GA	Gestational age
MRI	Magnetic resonance imaging
VLBW	Very low birth weight
VPT	Very preterm

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Methods

Participants born <30 weeks' GA and/or <1250 g were prospectively recruited into the Victorian Infant Brain Study cohort from the Royal Women's Hospital in Melbourne, Victoria, Australia. From July 2001 to December 2003, infants without severe congenital abnormalities were eligible for the study, and 227 who survived the neonatal period were recruited. Two children died in early childhood, leaving 225 survivors. Seventy-seven healthy control children born at term (37-42 weeks' GA) and of normal birth weight (≥2500 g) were also recruited from the Royal Women's Hospital, Maternal and Child Health Centers, and from the community. Forty-six of the control children were recruited during the neonatal period and had an MRI scan as part of the study protocol, and 31 were recruited at age 2 years with no neonatal MRI scan. At each follow-up, families were offered financial compensation for travel costs.

Children were assessed in the neonatal period, and were subsequently followed up at ages 2, 5, and 7 years. At the 7-year follow-up, 198 (88% of survivors) VPT/VLBW and 70 (91%) term children were assessed. The study was approved by the Human Research and Ethics Committees of the Royal Women's Hospital and the Royal Children's Hospital, and written consent was obtained from the parents.

At term-equivalent age, T_1 and T_2 images were acquired with a 1.5 Tesla MRI scanner (Signa LX Echospeed System; General Electric, Fairfield, Connecticut). Infants were placed unsedated in a Vac Fix beanbag (S&S Par Scientific, Odense, Denmark) to reduce motion. White matter abnormality was rated by a neurologist blind to birth group using a modified version of a rating system described previously.[10,14] This modified version has high intra-and inter-rater reliability, with intra-class correlation coefficients above 0.90. Six areas were rated, namely cystic lesions (score 0-4), focal signal abnormality (score 0-3), delayed myelination (score 0-2), callosal thinning (score 0-2), lateral ventricle volume (score 0-3), and white matter volume (score 0-3). The total score ranged from 0-17, with 0 indicating no white matter abnormality. Neonatal white matter data were collected for 191 VPT/VLBW children and 43 term children.

As part of the 2-year follow-up, parents completed a questionnaire to assess family social risk based on family structure, education of the primary caregiver, occupation of the primary income earner, employment status of the primary income earner, language spoken at home, and maternal age at birth.[17] Scores ranged from 0-12, with high scores representing greater social disadvantage.

At the 7-year follow-up, language was assessed as part of a larger neuropsychological battery. Five subdomains of language were assessed with a variety of standardized tests, each with acceptable test-retest reliability and content validity[18-20]: phonological awareness was assessed with the Phonological Processing subtest of the *NEPSY-II*[20]; semantics with the Language Content Index from the *Clinical Evaluation of Language Fundamentals-Fourth Edition* (CELF-4), Australian Standardized Edition[19]; grammar with the Language Structure Index from the CELF-4; discourse with the Making Inference subtest from the Test of Language Competence-Expanded Edition[18]; and pragmatics with the Pragmatics Profile questionnaire from the CELF-4. The first 4 subdomains were assessed by a trained clinician who was blinded to previous details of the children, whereas the Pragmatics Profile was completed by the parents. All test results are reported using scaled scores based on the child's age corrected for prematurity, with the exception of the Pragmatics Profile, which is reported as a total raw score (as normative data are unavailable).

Children who were too impaired to perform or understand a particular test were assigned a scaled score lower than the lowest possible scaled score for the subdomains of semantics, grammar, and discourse, to reflect a raw score of 0, and they were assigned a scaled score of 1 for the test of phonological awareness, which is the equivalent of a raw score of 0 in the norms table. It was not possible to assign a score to those children whose impairment meant the Pragmatics Profile was not appropriate because there is no scaled score equivalent. The number of children in the VPT/VLBW sample with available language data was 193 of the 198 followed up at age 7, where 5 children were excluded primarily because of incomplete assessments. All 70 term children had available language data.

Statistical Analyses

Data were analyzed with Stata/IC 12.0 for Windows (StataCorp, College Station, Texas). Differences between the VPT/VLBW and term samples on neonatal and demographic variables were analyzed using simple linear regressions or Mann-Whitney U tests for continuous variables, and χ^2 analyses or Fisher exact tests for categorical variables. Actual *P* values were reported for all analyses, with an α-level of 0.05.

To examine the differences between the VPT/VLBW and term samples on the 5 language subdomains, a simple linear regression was conducted for each subdomain using birth group as the predictor. These regression models were also fitted controlling for social risk score. To account for the nonindependent effect of twins/triplets from the same family, robust SEs using the Huber/White/sandwich method were used for all analyses. To examine whether group differences were due to children who were expected to have reduced language for reasons other than prematurity, analyses were repeated with the following children excluded: those who spoke languages other than English at home (VPT/VLBW n = 22; term n = 5), had evidence of a hearing impairment from auditory brainstem response at birth or audiometry during childhood (VPT/VLBW n = 20; term n = 1), or experienced significant developmental difficulties at 7 years (ie, Full-Scale IQ below 70 on the Wechsler Abbreviated Scale of Intelligence, and/or a diagnosis of a pervasive developmental disorder, and/or a diagnosis of severe cerebral palsy at age 7 years; VPT/VLBW n = 17); some children had more than 1 reason for exclusion. The

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