Associations of Newborn Brain Magnetic Resonance Imaging with Long-Term Neurodevelopmental Impairments in Very Preterm Children

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Objective To determine the relationship between brain abnormalities on newborn magnetic resonance imaging (MRI) and neurodevelopmental impairment at 7 years of age in very preterm children.

Study design A total of 223 very preterm infants (<30 weeks of gestation or <1250 g) born at Melbourne's Royal Women's Hospital had a brain MRI scan at term equivalent age. Scans were scored using a standardized system that assessed structural abnormality of cerebral white matter, cortical gray matter, deep gray matter, and cerebellum. Children were assessed at 7 years on measures of general intelligence, motor functioning, academic achievement, and behavior.

Results One hundred eighty-six very preterm children (83%) had both an MRI at term equivalent age and a 7-year follow-up assessment. Higher global brain, cerebral white matter, and deep gray matter abnormality scores were related to poorer intelligence quotient (IQ) (*P*s < .01), spelling (*P*s < .05), math computation (*P*s < .01), and motor function (*P*s < .001). Higher cerebellum abnormality scores were related to poorer IQ (*P* = .001), math computation (*P* = .018), and motor outcomes (*P* = .001). Perinatal, neonatal, and social confounders had little effect on the relationships between the MRI abnormality scores and outcomes. Moderate-severe global abnormality on newborn MRI was associated with a reduction in IQ (–6.9 points), math computation (–7.1 points), and motor (–1.9 points) scores independent of the other potential confounders.

Conclusions Structured evaluation of brain MRI at term equivalent is predictive of outcome at 7 years of age, independent of clinical and social factors. *(J Pediatr 2017;187:58-65).*

Approximately 10% of very preterm children (<32 weeks of gestation) develop significant impairments, such as cerebral palsy, while an additional 50% develop cognitive, motor, academic, or behavioral problems.[1] Perinatal factors related to adverse outcomes in very preterm children include lower gestational age (GA),[2] bronchopulmonary dysplasia,[3] infection,[4] intrauterine growth restriction,[5] moderate to severe brain injury on cranial ultrasound,[6] postnatal corticosteroid use,[7] and surgery as a newborn.[8] Despite the association of these clinical factors with adverse outcome, it remains challenging to predict impairment in individuals. A better understanding of the underlying nature of cerebral injury and altered brain development in very preterm infants may assist in identification of neurodevelopmental risk.

Magnetic resonance imaging (MRI) in the newborn period has improved awareness of brain injury and aberrant brain growth in very preterm infants[9-11] and may enhance the ability to predict neurodevelopmental outcomes. Common features on structural MRI in very preterm infants at term equivalent age include loss of white matter with enlarged lateral ventricles, signal abnormality in the white matter, delayed myelination, thinning of the corpus callosum, delayed cortical folding, and larger extracerebral space.[12,13] We have reported that quantitative scoring of these abnormalities was related to cognitive and motor delay at 24 months, even after taking into account other medical risk factors.[14] Others have reported the associations

CBL	Cerebellum
CGM	Cortical gray matter
CWM	Cerebral white matter
DGM	Deep gray matter
GA	Gestational age
IQ	Intelligence quotient
IVH	Intraventricular hemorrhage
MABC2	Movement Assessment Battery for Children, 2nd Edition
MRI	Magnetic resonance imaging
PVL	Periventricular leukomalacia
SDQ	Strengths and Difficulties Questionnaire

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of white matter abnormalities to cognitive, language, and motor deficits in older children using similar scoring systems.[15,16] For a more comprehensive evaluation of the nature of brain abnormalities in the very preterm infant, we developed a new scoring system[17] that included an evaluation of the cerebellum (CBL) and deep gray matter (DGM), which are both vulnerable to injury following very preterm birth. In addition, brain growth and ventricular size are measured rather than subjectively assessed.

The current study aimed to determine the relationship between this more expanded objective scoring of structural brain abnormalities and neurodevelopmental outcome at 7 years of age in very preterm children. We hypothesized that newborn MRI abnormalities, including those relating to the DGM and CBL, would be associated with adverse school-aged outcomes independent of the effect of other prognostic perinatal variables.

Methods

Participants comprised children born <30 weeks of GA or <1250 g birth weight between July 2001 and December 2003 from the Royal Women's Hospital in Melbourne, Australia. Two hundred twenty-seven very preterm infants without a congenital abnormality known to affect development were originally recruited (67% recruitment rate); 2 infants later died, and 2 were later excluded because of a subsequent diagnosis of a congenital abnormality, leaving 223 very preterm infants.

All infants had a brain MRI as close as possible to their expected due date; those who had their scan between 38 and 42 weeks of postmenstrual age were included in this study (n = 211), of whom 186 (88%) were reviewed at age 7 years (9 withdrew, 10 declined 7-year assessment, 3 could not be contacted, and 3 had emigrated).

The study was approved by the Human Research Ethics Committees of the Royal Women's Hospital and the Royal Children's Hospital in Melbourne, Australia. Written informed consent was obtained from parents before data collection. Information on this follow-up study have been published previously.[18-21]

MRI

Infants were scanned without sedation in a 1.5-T General Electric MRI scanner (Signa LX Echospeed System; General Electric, Fairfield, Connecticut). Infants underwent T_1-weighted (0.8- to 1.6-mm coronal slices; flip angle 45°; repetition time 35 ms; echo time 9 ms; field of view 21 × 15 cm^2; matrix 256 × 192), and T_2/proton density-weighted (1.7- to 3-mm coronal slices with axial and sagittal reconstructions at 3 mm slices; repetition time 4000 ms; echo time 60/160 ms; field of view 22 × 16 cm^2; matrix 256 × 192, interpolated to 512 × 512) sequences.

A standardized scoring system was used to assess the presence and severity of abnormalities in cerebral white matter (CWM), cortical gray matter (CGM), DGM, and CBL.[17] The system extends that described by Inder et al[12] by adding scales for assessing DGM and CBL, and integrates quantitative biometrics. The CWM scale (range 0-17) is the sum of 6 subscales assessing the presence and severity of cystic lesions, signal abnormality, myelination delay, thinning of the corpus callosum, lateral ventricle dilatation, and volume reduction. Scores <3 were categorized as normal, 3-4 were categorized as mild abnormality, and >4 were categorized as moderate to severe abnormality. The CGM scale (range 0-9) is the sum of 3 subscales assessing signal abnormality, delayed gyral maturation, and increased extracerebral space. The DGM and CBL scales (range from 0-7) have 2 subscales assessing signal abnormality and volume reduction. For the CGM, DGM, and CBL abnormality scales, scores of 0 were categorized as normal, 1 as mild abnormality, and >1 as moderate to severe abnormality. A global brain abnormality score (range 0-40) is generated by summing the CWM, CGM, DGM, and CBL scales. For the global brain scale, scores <4 were categorized as normal, 4-7 as mild abnormality, and >7 as moderate to severe abnormality. Scans were reviewed by an experienced neonatal neurologist independent of knowledge of long-term outcomes, with excellent interrater and intrarater reliabilities (intraclass correlation coefficient > 0.90).[17]

Neurodevelopmental Assessment

At 7 years' corrected age, general intelligence, academic achievement, motor functioning, and behavior were assessed. General intellectual functioning was assessed using the full scale intelligence quotient (IQ) of the Wechsler Abbreviated Scale of Intelligence.[22] Word reading, spelling, and math computation were assessed with the Wide Range Achievement Test-4.[23] Motor skills were assessed using the Movement Assessment Battery for Children-Second Edition.[24] Parents rated their child's behavior using the Strengths and Difficulties Questionnaire (SDQ).[25] The total difficulty score of the SDQ was used as an estimate of behavioral problems, with a higher score reflecting greater behavioral difficulty (range: 0-40). Age standardized scores are reported for the Wechsler Abbreviated Scale of Intelligence (mean = 100, SD = 15), Wide Range Achievement Test-4 (mean = 100, SD = 15), and Movement Assessment Battery for Children, Second Edition (mean = 10, SD = 3) based on the child's corrected age to avoid bias in cognitive test scores.[26] The SDQ does not provide age standardized scores, and raw scores are reported. Children who did not complete the test because it was too difficult were assigned a score that was 3 SD below the normative mean for that test (or above 1 SD for the SDQ). Assessments were performed by trained assessors who had no knowledge of the child's medical history or newborn MRI.

Outcome Risk Factors

Perinatal data were obtained from chart review, and sociodemographic information was obtained from a caregiver questionnaire. Birth factors include antenatal corticosteroid exposure, multiple birth, sex, GA, and birth weight standardized for GA and sex (birth weight z score).[27] Neonatal factors included grade 3 or 4 intraventricular hemorrhage (IVH), cystic periventricular leukomalacia (PVL), bronchopulmonary dysplasia (defined as the requirement for oxygen at 36 weeks of