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Advanced neuroimaging and its role in predicting neurodevelopmental outcomes in very preterm infants

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ABSTRACT

Up to 35% of very preterm infants survive with neurodevelopmental impairments (NDI) such as cognitive deficits, cerebral palsy, and attention deficit disorder. Advanced MRI quantitative tools such as brain morphometry, diffusion MRI, magnetic resonance spectroscopy, and functional MRI at term-equivalent age are ideally suited to improve current efforts to predict later development of disabilities. This would facilitate application of targeted early intervention therapies during the first few years of life when neuroplasticity is optimal. A systematic search and review identified 47 published studies of advanced MRI to predict NDI. Diffusion MRI and morphometry studies were the most commonly studied modalities. Despite several limitations, studies clearly showed that brain structural and metabolite biomarkers are promising independent predictors of NDI. Large representative multicenter studies are needed to validate these studies.

Introduction

Every year in the United States, more than 100,000 babies are born very preterm (at ≤32 weeks gestational age). Up to 35% of these infants develop cognitive, behavioral, and/or psychological abnormalities and 10% develop cerebral palsy (CP), thereby increasing their risk for poor educational, health, and social outcomes.[1–3] The continuing high incidence of preterm births in the United States and worldwide—1 out of every 9 births[4]—coupled with improving survival rates that exceed 90% in developed countries is contributing to an increased prevalence of survivors with such neurodevelopmental impairments (NDI).[5,6] The societal economic impact of lifetime care for persons born with CP and cognitive deficits in the United States is estimated to be $15 billion and $64 billion annually, respectively.[7]

Children with CP typically do not receive a clinical diagnosis until 2 years of age. Cognitive deficits and behavioral/psychological abnormalities cannot be reliably diagnosed until 3–5 years of age.[8–10] Yet, in the first 3 years after birth, the brain undergoes dramatic growth, and trillions of synaptic connections are laid down.[11] These sensitive early years are critical for neuroplasticity.[12] Early diagnosis of developmental disabilities using traditional means is however unlikely because neurologic function is still very immature at birth. Development of imaging prognostic biomarkers at birth could fill this critical need for early diagnosis. Such an advance would facilitate targeted delivery of evidence-based

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infant stimulation programs or new neuroprotective interventions[13–15] after neonatal intensive care unit (NICU) discharge to preserve brain development and/or promote neuroplasticity. Prognostic biomarkers could also be developed into surrogate endpoints of NDI at term-equivalent age (TEA) for more efficient testing of neuroprotective clinical trials during the initial neonatal intensive care stay.

How accurately do existing biomarkers or statistical models in the neonatal period predict NDI in very preterm infants? Several large studies from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Neonatal Research Network have attempted to answer this question using clinical risk factors at the time of preterm birth, during the NICU hospitalization, and at NICU discharge.[16–18] Two of these studies also developed risk prediction calculators to help clinicians counsel families about their infant's risk of NDI.[16,17] While these studies did improve prediction accuracy over existing prognostic models, they are still unable to accurately identify eligible babies for early intervention therapies and neurodevelopmental follow-up. Further, they did not examine the value of conventional structural MRI (sMRI) during the initial NICU hospitalization or at TEA. Hintz et al.[19] examined the incremental value of sMRI over clinical factors and early and late cranial ultrasound (US) findings in predicting NDI or death at 18–22 months' corrected age (CA) in 480 extremely preterm infants. The addition of sMRI had only a small impact on prediction accuracy because most major lesions other than cerebellar hemorrhages were readily visible on cranial US. These results are similar to other large qualitative sMRI studies[20] and to a recent meta-analysis of all sMRI studies at TEA in very preterm infants.[21] This meta-analysis examined the prognostic value of white matter abnormalities on term MRI to predict individual and combined NDIs. For moderate to severe WMA, the sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio to predict CP at $\geq$18 months was, 67%, 92%, 8.1, and 0.4, respectively and for mental development was, 38%, 87%, 3.0, and 0.7, respectively. Prognostic test properties for a qualitative diagnosis of diffuse excessive high signal intensity (DEHSI) in predicting NDI were even lower.[21]

Clearly, a critical gap continues to exist and there is an urgent need for more effective imaging tools and early prognostic biomarkers. In order to improve prediction accuracy, such biomarkers have to be objective, thereby reducing or ideally eliminating measurement error. They also need to be sensitive, so that subtle structural and functional connectivity and metabolic abnormalities can be accurately diagnosed. Advanced MRI techniques such as volumetric MRI (vMRI), diffusion tensor imaging and diffusion MRI (dMRI), magnetic resonance spectroscopy (MRS), and resting-state functional connectivity MRI (fcMRI) appear to be ideally suited to address these needs (see Toa and Neil[22] for a technical review). Each of these modalities appears to be more sensitive than sMRI and able to offer complementary brain measurements such as regional volumes, metabolites, microstructural connectivity, and functional network connectivity. The image analysis tools for these novel technologies are increasingly being automated, thereby eliminating subjective human assessments. Their quantitative nature lends far greater study power as compared to categorical measures from cranial US and sMRI. The higher reliability and reduced measurement error also increase study power and improve prediction validity. Overall, these advanced modes of MRI give the best opportunity to identify and develop powerful prognostic biomarkers and surrogate endpoints for clinical trials. The goal of this review is to determine the independent ability of advanced brain MRI biomarkers at TEA to predict NDI in very preterm infants.

Methods

A systematic search strategy was employed to identify and critique all published early advanced MRI studies that predicted one or more neurodevelopmental impairments at 18 months CA or later in very preterm infants. The following inclusion criteria and definitions were used to select eligible studies: (1) very preterm infants, born at or below 32 weeks gestational age (GA) or very low-birth-weight infants (BW $<$ 1500 g); (2) advanced brain MRI: any MRI study that performed dMRI, MRS, fMRI, or quantitative measures of brain macrostructure (morphometry) or lesions; (3) TEA: 37–42 weeks postmenstrual age (PMA); and (4) neurodevelopmental impairment: CP, cognitive or intellectual impairments, social–emotional problems, and/or behavioral/psychological abnormalities diagnosed at a minimum age of 18 months CA or later. Additionally, only longitudinal cohort, nested cohort, and case–control studies were included in the analyses. A few studies that predominantly studied very preterm or very low-birth-weight infants but also included slightly more mature infants (e.g., 33 and 34 weeks' GA) were permitted for inclusion. Only full-text articles were included in this study.

Medline/PubMed database was searched on 3/15/16 using the following systematic search strategy that included Medical Subject Heading (MeSH) and few non-MeSH search terms: ("infant, premature" OR "infant, low-birth-weight") AND ("diffusion tensor imaging" OR "diffusion magnetic resonance imaging" OR "connectome" OR "DTI" OR "diffusion tensor tractography" OR "DTT" OR "functional neuroimaging" OR "magnetic resonance imaging" OR "fMRI" OR "fcMRI" OR "functional connectivity" OR "magnetic resonance spectroscopy" OR "brain/metabolism" OR "brain mapping" OR "brain volume") AND ("neurodevelopmental disorders" OR "developmental disabilities" OR "disability evaluation" OR "cerebral palsy" OR "motor disorders" OR "cognition disorders" OR "cognitive" OR "intellectual disability" OR "intelligence" OR "language development disorders" OR "Bayley" OR "behavior" OR "mental competency" OR "mental disorders" OR "autism spectrum disorder" OR "autistic disorder" OR "attention deficit disorder with hyperactivity" OR "ADHD" OR "child behavior disorders"). The PsycINFO database was also searched for additional relevant articles.

Retrieved articles were screened based on the title and abstract for definite exclusions. For the remainder, full text of each article was accessed and the eligibility criteria applied. Last, the bibliography of all eligible full-text articles was hand-searched for additional eligible articles. Eligible articles were critically appraised using the Critical Appraisal