

Automated Quantification of Diffuse White Matter Abnormalities in Very Preterm Infants Predicts Language and Cognitive Development at Two Years of Age

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INTRODUCTION

More than 100,000 very preterm infants (VPI, ≤ 32 weeks gestational age) are born every year in the United States. By school age, 30-50% of them exhibit cognitive deficits. The diagnosis of the deficits cannot be made until early childhood. There is a critical need to identify the highest risk VPI to facilitate the appropriate assignment of early intervention resources, the enhancement of the effectiveness of infant stimulation programs and the improvement of infant selection for neurodevelopmental follow-up. The significance of diffuse white matter signal abnormality (WMSA) on conventional T2-weighted MRI at around term-equivalent age [1] as a predictor of later cognitive impairment remains unclear. A few studies have observed a significant negative association between WMSA and with neurodevelopmental outcome [2-4]. Conversely, others have not observed the association [5-7]. The limited progress in resolving the above question can partly be attributed to the use of conventional qualitative MRI readings. Such an approach remains subjective and lacks sufficient reliability for accurate and reproducible WMSA diagnosis and may therefore contribute to suboptimal neurodevelopmental outcome prediction. In this work, based on a prospective cohort of VPI infants, we demonstrated a significant correlation between objectively quantified WMSA volumes and language as well as cognitive developmental scores on the third edition of the Bayley Scales of Infant and Toddler Development at two years of age.

METHODS

The Children's Memorial Hermann Hospital (CMHH) and The University of Texas Medical School at Houston joint institutional review board (IRB) approved the study. Written informed consent for each infant was obtained prior to enrollment in the study. The study population was derived from a cohort of 50 VPIs without any major congenital anomalies, cared for in the NICU of CMHH from 2007 to 2009. Their mean (standard deviation [SD]) gestational age was 25.5 (1.6); birth weight was 750.8 (143.1) grams; and the postmenstrual age at MRI was 38.7 (2.3). All infants were imaged with a 3 T Philips scanner using a dual-echo fast-spin-echo sequence with use of an eight-channel SENSE-compatible phased array receive head coil. The imaging parameters used were: TE1 = 8.75ms; TE2 = 175 ms; TR = 10,000 ms; flip angle = 90°; FOV = 180x180 mm²; the imaging matrix = 256x256 mm²; slice thickness = 2 mm. All infants were transported to the MRI scanner by an experienced neonatal transport nurse after feeding, swaddling and placement of silicone ear plugs (E.A.R. Inc., Boulder, CO) and Natus MiniMuffs (Natus Medical Inc., San Carlos, CA) to facilitate natural sleep and attenuate MRI noise. Sedation was not used for any of the cases. The segmentation of cerebral tissues (white matter and gray matter) was achieved by incorporating the segmentation from SPM8 software (Wellcome Department of Imaging Neuroscience, University College London) with anatomical information obtained from an infant probabilistic brain atlas. The atlas was built from a set of 19 manual parcellations of ELBW brains randomly selected from our cohort [8]. We then defined WMSA to be voxels with intensity values greater than or equal to 1.4 SD above the mean of cerebral matter tissue, following the same strategy as described in [9]. Cognitive and language developments at 2 years of age were evaluated using standardized Bayley scales of Infant and Toddler Development III (BSID-III). In this work, we will investigate the relationship of developmental outcomes with WMSA regional volumes defined at level of the 1. Entire WM; 2. Periventricular WM – on slices beginning with the first appearance of the frontal horns and ending with the last images of the midbody of the lateral ventricles; and 3. Centrum semiovale – defined as the two axial slices above the last slice of the midbody of the lateral ventricles.

RESULTS

WMSA volume was quantified by taking the product of total number of positive voxels in the detected binary mask by the volume of each voxel. Computer simulations showed that accuracy rates were over 95% and false detection rates were below 5% [8]. Representative images from one VPI with objective WMSA detection highlighted in red are presented in Fig. 1. Twelve infants were excluded from the study due to the lack of Bayley scores, or severe encephalomalacia or excessive motion artifacts. Therefore, 38 VPIs were available for full analysis. The relationships between continuous variables of objectively quantified WMSA volumes vs. BSID-III language and WMSA volumes vs. BSID-III cognitive scores were identified using both Pearson correlation and simple linear regression analyses. Assumptions of both analyses were tested and met. Correlational statistical analyses showed that BSID-III language and cognitive scores were significantly (P value < 0.05) correlated with total WMSA volume as well as WMSA within the sub-regions of WM (Fig. 2). WMSA at the level of the centrum semiovale exhibited the strongest linear correlation with Bayley scores, while WM in the periventricular crossroads exhibited the weakest correlation. With increasing WMSA volumes, both cognitive and languages scores decrease at 2 years of age. We also observed that WMSA volumes exhibited a tighter correlation with language than cognitive scores. In bivariate analyses, sex, gestational age, and postmenstrual age at MRI scan were not significant and exerted minimal influence on the beta coefficients.

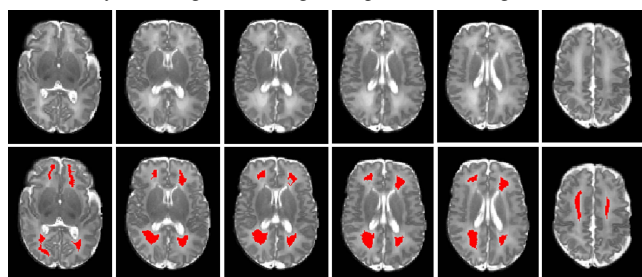


Figure 1. Automated WMSA detection at six different axial levels. Top row: T2-weighted images; bottom row: detected WMSA marked in red. The automated detections closely approximated the visually apparent signal abnormalities.

CONCLUSIONS

In our cohort of very preterm infants, we demonstrated automatically detected WMSA volume on term-equivalent age MRI to be a significant predictor of cognitive and language development at 2 years of age. Prior efforts to correlate WMSA with cognitive outcomes may have failed due to the low reliability of diagnosing WMSA qualitatively. Our findings support the use of objective automated techniques to accurately quantify the lesion burden in perinatal-neonatal brain injury. Furthermore, lesion localization appears important in distinguishing developmentally normal from pathologic signal abnormalities, as observed in the periventricular crossroads and centrum semiovale regions, respectively. This also facilitates improved outcome prediction. Our work will facilitate population-based studies to more accurately characterize WMSA's long-term sequelae.

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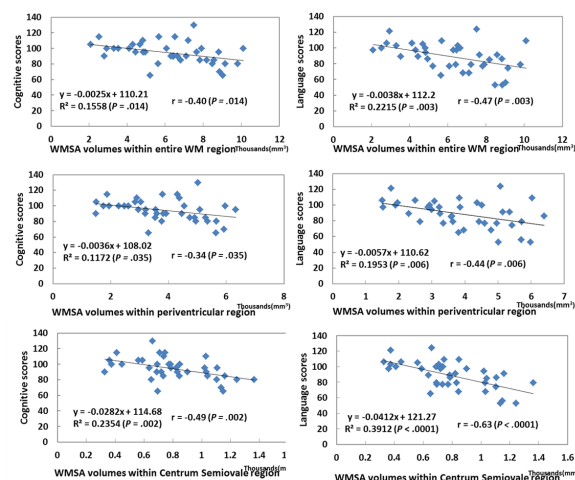


Figure 2. Linear regression and Pearson correlation analyses of automated quantified WMSA within different WM regions and Bayley III cognitive and language scores. R^2 denotes linear regression's coefficient of determination and r denotes Pearson correlation coefficient. Larger WMSA volumes correspond with both lower cognitive and language scores. WMSA regional volume within centrum semiovale is a better predictor of Bayley scores than WMSA volumes within the periventricular WM regions.