Sex Differences in Outcome and Associations with Neonatal Brain Morphology in Extremely Preterm Children

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Objective To investigate sex differences in neurologic and developmental outcomes in extremely preterm (EPT) children and explore associations with neonatal brain morphology.

Study design A population-based cohort of infants born at <27 weeks gestation underwent magnetic resonance imaging (MRI) at term equivalent age (n = 107). Voxel-based morphometry (n = 27) and tract-based spatial statistics (n = 29) were performed in infants with normal MRI findings. Neurologic and developmental assessment (using the Bayley Scales of Infant and Toddler Development–Third Edition [BSITD-III]) was performed at 30 months corrected age (n = 91).

Results EPT boys had lower mean cognitive composite scores (P = .03) and lower mean language composite scores (P = .04) compared with EPT girls. Rates of cerebral palsy were similar in the 2 sexes. No perinatal factor explained the variance in outcomes. Visual inspection of T1- and T2-weighted MRI images found that delayed myelination was found more frequently in boys, whereas cerebellar abnormalities were more common in girls. In the subgroup of children with normal MRI findings (n = 27), boys had poorer cognitive function (P = .015) and language function (P = .008), despite larger volumes of cerebellar tissue (P = .029). In boys, cerebellar volume was positively correlated with BSITD-III cognitive and motor scores (P = .04 for both). In girls, white matter volume (P = .02) and cortical gray matter volume (P = .03) were positively correlated with BSITD-III language score. At the regional level, significant correlations with outcomes were found only in girls.

Conclusion Cognitive and language outcomes at age 30 months were poorer in boys. Sex-related differences were observed on neonatal structural MRI, including differences in the patterns of correlations between brain volumes and developmental scores at both global and regional levels. *(J Pediatr 2014;164:1012-8)*.

The male disadvantage with regard to perinatal morbidity and mortality is well known.[1] In preterm infants, follow-up data from several cohorts have revealed significant differences in outcomes between the sexes.[2,3] The higher incidence of brain lesions, such as intraventricular hemorrhage and periventricular leukomalacia, in male preterms[2,4] explains some, but not all, of these differences. For example, in extremely preterm (EPT) infants with normal head ultrasound, male sex was shown to be an independent risk factor for a low mental developmental index at age 18-22 months.[5] Magnetic resonance imaging (MRI) in preterm adolescents has demonstrated sex-based differences in brain microstructure and volume in the absence of overt perinatal injury.[6]

We previously reported MRI data in a population-based cohort of EPT infants[7] and found significant associations between neonatal white matter abnormalites identified by visual inspection of structural MRI and adverse outcomes.[8] Others have demonstrated relationships between neonatal brain tissue volumes and neurodevelopmental outcomes.[9] Furthermore, a study using Tract-Based Spatial Statistics (TBSS, a tool for analyzing diffusion tensor imaging [DTI] data) performed in the neonatal period suggested an association between white matter structural alterations and toddler age outcomes in preterm infants.[10] The aim of the present study was to investigate sex differences in neurologic and developmental outcomes in a cohort of EPT children, and explore associations with brain structure as assessed by MRI at term equivalent age.

Methods

Study subjects were participants in the Extremely Preterm Infants in Sweden Study (EXPRESS) project,[11] a prospective population-based study of EPT infants in

BSITD-III	Bayley Scales of Infant and Toddler Development–Third Edition
CP	Cerebral palsy
CPAP	Continuous positive airway pressure
DTI	Diffusion tensor imaging
EPT	Extremely preterm
EXPRESS	Extremely Preterm Infants in Sweden Study
MRI	Magnetic resonance imaging
TBSS	Tract-Based Spatial Statistics

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Sweden investigating neurodevelopmental outcomes at 30 months corrected age, with a subcohort in Stockholm undergoing MRI at term equivalent age.[8] All infants born between January 2004 and April 2007 at gestational age <27 weeks + 0 days were eligible for inclusion in the study (Figure 1). Children with malformations, chromosome aberrations, malignant disorders, or congenital infections were excluded. Perinatal data were collected prospectively (Table I). The regional Ethics Committee in Stockholm approved the study, and informed consent was obtained from parents of all subjects.

MRI at Term Equivalent Age

MRI was performed with a Philips Intera 1.5-T system (Philips, Eindhoven, The Netherlands) and consisted of sagittal T1- weighted and T2-weighted turbo spin echo images, axial T2*-weighted images, axial inversion recovery images, and a 3-dimensional T1-weighted gradient echo image. The diffusion-weighted MRI images were acquired with 15 directions, b value = 700 s/mm^2, voxel size = 1.4 × 1.4 × 2.2 mm^3, and one b = 0 image in the axial plane, as described previously.[7] The T1-weighted and T2-weighted images were visually inspected by 4 independent observers according to a standardized scoring system for structural abnormalities.[12] Five separate white matter variables were assessed: abnormal white matter signal, reduction in white matter volume, cystic changes, ventricular dilatation, and thinning of the corpus callosum/myelination (with myelination deemed normal if reaching the central corona radiata, caudate nucleus, and centrum semiovale; mildly delayed if reaching the posterior limb of the internal capsule, lenticular nucleus, and thalamus; and severely delayed if reaching only the brainstem and cerebellum). From the summed individual item scores, a composite score was derived. Based on this composite score, the study group was divided into 4 subgroups: (1) no white matter abnormalities; (2) mild white matter abnormalities; (3) moderate white matter abnormalities; and (4) severe white matter abnormalities. Similarly, gray matter was assessed for abnormal signal in the cortical or deep gray matter, enlargement of the subarachnoid spaces, and delayed gyral maturation. Infants were then divided into those with normal gray matter and those with abnormal gray matter based on the calculated composite score. The agreement rate between observers was 98% for group assignment, and consensus was reached after discussion when opinions differed.

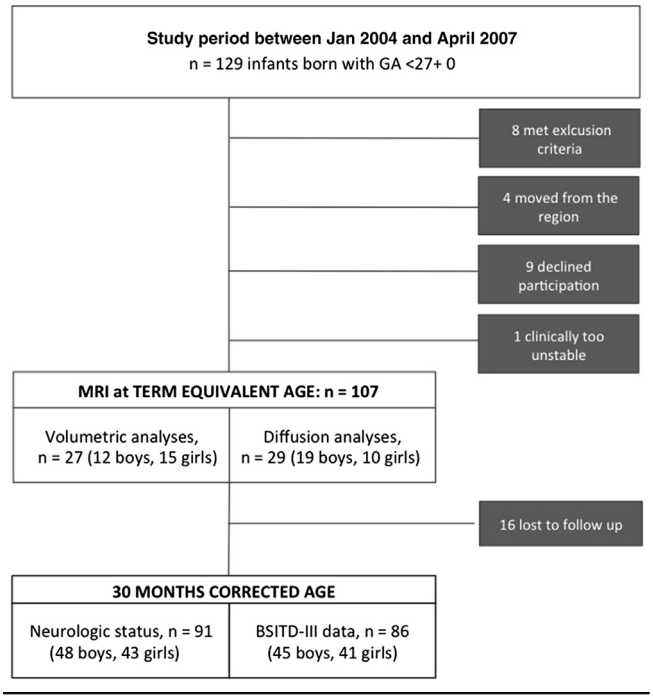

Figure 1. Study population.

In addition to the scoring, a standard radiologic assessment of MRI images was performed, assessing for malformations, the presence of hemosiderin, and cerebellar abnormalities, such as cysts, hemosiderin, atrophy, and abnormal signal intensity. Quantitative analyses were performed on MRI data of the infants without moderate to severe white matter abnormalities or gray matter abnormalities based on the scoring system, or without cerebellar abnormalities. Automatic segmentation of brain tissues was performed using SPM8 software (http://www.fil.ion.ucl.ac.uk/spm) running in MATLAB version 7.5 (MathWorks, Natrick, Massachusetts) with specific neonatal priors,[13] including white matter, cortical and deep gray matter, cerebrospinal fluid, the whole cerebellum, and brainstem. (The latter 2 structures were not segmented into gray matter and white matter.) A Diffeomorphic Anatomical Registration through an Exponentiated Lie algebra algorithm was applied to improve the intersubject registration. Images were modulated and smoothed with a full width at half-maximum of 3-mm Gaussian kernel for white matter, cortical and deep gray matter, whole cerebellum, and brainstem. Volumes (mm^3) for the segmented/normalized/modulated images were obtained with the Easy Volume toolbox.[14]

Diffusion-weighted MRI data were corrected for movement and eddy current artifacts and fitted to a tensor model, and fractional anisotropy maps and apparent diffusion coefficient maps were calculated. To investigate differences in apparent diffusion coefficient and fractional anisotropy between groups across the whole brain, diffusion data were processed using FMRIB's Diffusion Toolbox (version 2.0; Analysis Group, Oxford, United Kingdom) and analyzed with TBSS version 1.2 in FSL version 4.1.4 (Analysis Group).[15] The fractional anisotropy (and apparent diffusion coefficient) maps of all subjects were aligned into a standard space using nonlinear registration, and a mean fractional anisotropy skeleton was created representing the centers of major tracts common to the group of subjects. The fractional anisotropy skeleton was thresholded to fractional anisotropy ≥ 0.20 to include the major white matter tracts but exclude peripheral tracts where there was signficant intersubject variability and/or partial volume effects with gray matter. The aligned fractional anisotropy data of each subject were projected onto this skeleton perpendicular to the local tract direction, and the resulting data were fed into voxel-wise