The role of estradiol in preterm brain development

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Introduction: The preterm infant is at significant risk of brain injury and neurodevelopmental impairment. Previous studies have demonstrated that these infants experience a relative lack of estradiol in the ex-utero state, once the supply of placental estrogen is removed. In the animal model, estradiol has been shown to act as a trophic factor for developing neurons and can promote synapse formation in vitro. Sex specific differences in brain development have also been described, with estradiol having a "masculinizing" influence in the male brain but not the female brain.

Aim: Our aim was to prospectively investigate a cohort of preterm infants to determine whether levels of estradiol in the first six weeks of life were associated with volumetric or structural changes to the brain at term corrected age.

Methods: 130 preterm infants (gestational age at birth < 30 weeks) were enrolled into this study. Subjects had 0.5 ml of blood collected at birth from the cord and then on days 1, 4, 7, 14, 21, 28 and 42 of life in conjunction with routine blood testing. Blood was spun and the serum stored at -70 degrees C. Serum levels of estradiol (E2) were assayed in batches and a summary measure representing exposure to E2 was calculated by measuring area under the curve (AUC). At term corrected the infants were imaged with a 1.5 Tesla General Electric MRI Scanner. 3D MRI and image processing algorithms were used to perform quantitative volumetric analysis of brain images. T1 spoiled gradient recalled (SPGR) sequences (1.5mm coronal slices, flip angle 45°, repetition time 35ms; echo time 9ms; field of view 18cm; matrix= 256 x 256) and dual-echo (proton density and T2-weighted) spin echo sequences (3mm coronal; TR=4000msec; TE 60 / 160 msec; FOV 18cm; matrix 512 x 512, interleaved acquisition) were acquired. An image processing algorithm was used to segment the imaged volume[1]. Average cerebral tissue volumes were calculated for cortical gray matter (CGM), unmyelinated white matter (UMWM), myelinated white matter (MWM), basal ganglia (BG), cerebrospinal fluid (CSF), and intracranial volume (ICV). Spin echo line scan (b = 750 um2/ms) was performed from which the apparent diffusion coefficient (ADC), relative anisotropy (RA) and fractional anisotropy (FA) were calculated. These measures were calculated in the frontal, central and posterior white matter bilaterally (Figure 1). Statistical analysis was performed using SPSS for Windows, v 11.0.

Results: ***Volumetric analysis*****:** 130 preterm infants, 65 males and 65 females were recruited between July '02 and December '03.Their mean gestational age was 26.9 weeks and mean birth weight was 964 grams. 100 of the 130 had MR brain scans at term corrected and line scan diffusion imaging was performed on 52 infants. Total ICV and volume of CGM were significantly reduced with increasing E2 levels throughout the first 28 days (CGM p<0.02, ICV p<0.02 all times) (Figure 2). After adjustment for gestational age and ICV, E2 was significantly associated with reduced total volumes of UMWM and this was unrelated to gender.

Diffusion results**:** ADC in the central white matter was significantly associated with the level of E2 from the cord (p=0.01), day 1 (p=0.02), day 4 (p=0.01), day 7 (p=0.02) and the summary measure of AUC (p=0.009, Figure 3). Gender specific analysis revealed that the ADC in the central white matter was significantly associated with E2 for males, but not females. In the posterior white matter, RA was associated with E2 on day 4 (p=0.002). This association persisted strongly for males (p= 0.001) but was not evident for females (p= 0.12). The same relationship existed for FA and E2 on day 4 (males, p=0.001; females, p=0.14).

Conclusion: Estradiol exposure in the first 4 weeks of life following preterm birth appears to alter structural cerebral development by term equivalent. In all preterm infants, exposure to increased E2 levels was associated with a reduction in total ICV and CGM. In male preterm infants, diffusion measures in the white matter were also altered with increasing levels of E2 being significantly associated with elevations in ADC and reduction in FA measures. The alteration in white matter microstructure and CGM volumes in male preterm infants with higher estradiol levels may reflect a widespread disturbance in cerebral structural development. This may be the result of enhanced vulnerability to injury and/or altered cerebral development which may be gender specific for males exposed to estradiol. This cohort of infants will be followed until two years of age to determine the neurodevelopmental correlate of these hormone levels.

Figure 1

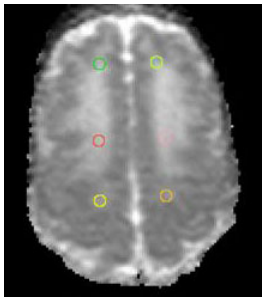


Figure 2

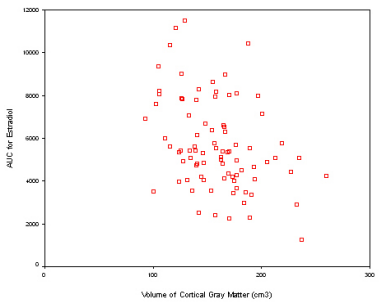
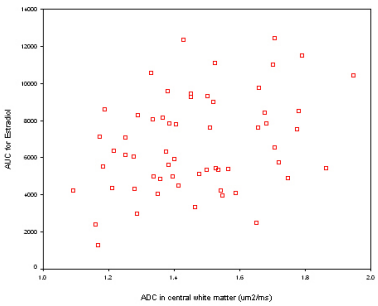


Figure 3



References:

1. Warfield SK et al. MIA Med Image Analysis 2000; 4: 43-55.

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