Long-term alterations of brain NAA, Cho and Cr in extremely preterm adolescents are associated with cognition

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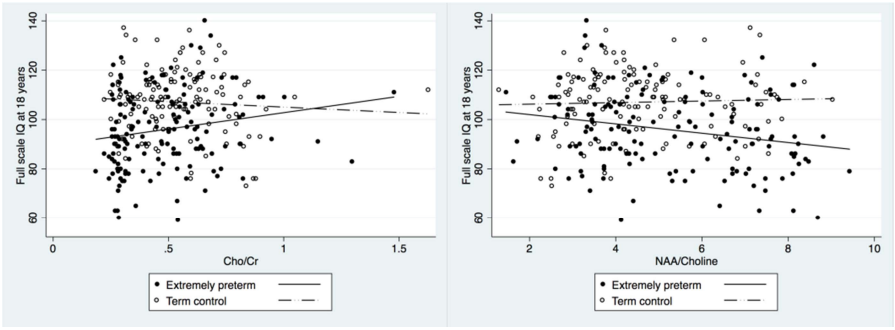
Introduction: Preterm birth is associated with increased risk of white matter (WM) injury resulting in disrupted WM maturation and neurodevelopmental deficits.Extremely preterm infants(EP; born <28weeks' gestation) are at increased risk of cerebral palsy, and other motor and cognitive impairments[1]. Simultaneously raised choline (Cho)/creatine (Cr) and reduced N-acetylaspartate (Naa)/Cho in posterior white matter, measured using ^{1}H Magnetic Resonance Spectroscopy (MRS),predict abnormal 1-year motor outcome in infants born very preterm (<32 weeks' gestation)[2]. It is unknown whether the relationship between ^{1}H MRS metabolite peak-area ratios with neurodevelopment persists into adolescence.We aimed to compare the metabolite ratios NAA/Cr, Cho/Cr and NAA/Cho between EP and term controls at age 18 years and to explore the association between these metabolite ratios and full scale IQ at 18 years.

Methods: 283 subjects, comprising a regional cohort of 150 EP adolescentsand 133 term controls born in 1991-92 in the state of Victoria, Australia, underwent MRS at 18 years of age. Studies were performed in 2 centres, each equipped with a Siemens 3T Magnetom Trio scanner. ^{1}H MRS was obtained from a 20x15x10 mm voxel centred on the left posterior cingulate (PC)WM using a 12 channel receive-only head coil and a PRESS acquisition (TR = 3000ms, TE = 135ms, 128 averages).Spectra were fitted using LCModel[3] and the metabolite ratios NAA/Cr, Cho/Cr and NAA/Cho were calculated. Statistics were performed using STATA 13.0 (StatCorp, Texas, USA). Ratios were compared between groups using t-tests and correlated with IQ (two-subtest version of the Wechsler Abbreviated Scale of Intelligence[4]) at 18 years using linear regression.

Results: Mean (SD) gestational age at birth, age at scan, IQ and metabolite ratios are shown in the Table. NAA/Cr and Cho/Cr were lower in EP subjects compared with controls, whereas NAA/Cho was higher. No correlation was seen between metabolite ratios and IQ in controls (Cho/Cr: R^2 = 0.004, coefficient (coeff) = -4.4, p = 0.49; Naa/Cr: R^2 = 0.012, coeff= 9.1, p = 0.25; Naa/Cho: R^2 = 0.001, coeff = 0.3, p = 0.40). Correlation coefficients were significantly different in EP subjects compared with controls for Cho/Cr and Naa/Cho, but not Naa/Cr; see figure (coefficients EP group, p-values for difference compared with controls: Cho/Cr: R^2 = 0.032, coeff = 13.2, p = 0.04; Naa/Cr: R^2 = 0.001, coeff = 3.1, p = 0.56; Naa/Cho: R^2 = 0.050, coeff = -1.9, p = 0.03)

	Gestation age at birth (weeks)	Age at scan (years)	IQ	Naa/Cr	Naa/Cho	Cho/Cr
EP (n=150)	**25.8 (1.0)**	**18.4 (0.8)**	**96 (16)**	**2.15 (0.18)**	**5.22 (1.90)**	**0.48 (0.22)**
Controls (n=133)	**39.3 (1.3)**	**18.0 (0.9)**	**107 (13)**	**2.20 (0.16)**	**4.95 (1.61)**	**0.54 (0.20)**
P-value	**< 0.001**	**0.35**	**< 0.001**	**0.03**	**0.003**	**0.02**



Discussion: This is the first study to report long term brain metabolite differences in PC WM in EP with Naa/Cr. Naa/Cho and Cho/Cr significantly different compared to controls. The PC cortex is a highly connected region and has an important role in cognition[5]. In EP subjects at term Cho/Cr is raised in those with poor motor outcomes[1]. However the current study shows that at age 18, Cho/Cr is decreased in EP subjects, suggesting an increased rate of aging related to a reduced turnover of cells[6].The correlations between IQ and MRS in EP subjects but not controls may help to further elucidate cognitive impairment associated with EP birth.

References

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