White matter fractional anisotropy (FA) in the assessment of treatment-induced neurotoxicity in childhood cancer survivors: association with neurocognitive function

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Introduction:

Treatment-induced neurotoxicity is a major cause of neurobehavioural morbidity in childhood cancer survivors. We have shown that white matter FA is reduced in childhood medulloblastoma survivors (1) and that the reduction correlates with known risk factors of neurotoxicity (2) suggesting that FA may be a biomarker of treatment-induced white matter damage. In a cohort of childhood medulloblastoma (MED) and acute lymphoblastic leukemia (ALL) survivors, we aim to determine if reduction in white matter FA correlates with neurocognitive function.

Methods:

Thirty childhood medulloblastoma (MED) and acute lymphoblastic leukemia (ALL) survivors previously healthy prior to diagnosis were enrolled. MED survivors were treated with surgery, standard chemotherapy and whole brain irradiation ($n=12$, age range: 6 yrs–20 yrs, dose range: 23.4Gy–40.0Gy) whilst ALL survivors were treated with standard systemic and intrathecal chemotherapy without ($n=9$, age range: 6.8yrs–17.7yrs) or with whole brain irradiation ($n=9$, age range: 7.4yrs–18.3 yrs, dose range: 12.0Gy–24.0Gy). Diffusion tensor MR imaging (DTI) was performed on a 1.5T imager using single-shot echo-planar imaging with TR=10000ms, TE=100ms, acquisition matrix=128 × 128, field of view =28cm, slice thickness of 5mm with 1.5mm gap, b factor=1200s/mm^2. Diffusion-sensitizing gradient encoding was applied in 25 directions. FA maps were generated (FUNCTOOL, GE Medical Systems). 31 controls subjects were imaged by the same protocol and divided into groups by age: 6–8 years old ($n=4$), 9–11 years old ($n=11$), 12–14 years old ($n=8$) and 15–20 years old ($n=8$). Mean white matter FA was computed for each subject by SPM2 (Wellcome Dept of Imaging Neuroscience, Institute of Neurology, UK), using the method previously described (2). Patient white matter FA was compared to the corresponding control age-group mean white matter FA in order to calculate percentage deviation in FA (Δ FA). Neurocognitive evaluations obtained at least one year after treatment, were performed within one year of DTI scans in all but one patient (mean: 124 days, range 0–476 days). Hong Kong Wechsler Intelligence Scale for Children (≤16 years old) and Wechsler Adult Intelligence Scale-Revised (> 16 years old) estimates for full-scale IQ (FSIQ), verbal IQ (VIQ) and performance IQ (PIQ) were derived from the following subsets; information, digit span, vocabulary, arithmetic, comprehension, similarities, picture completion, picture arrangement, block design, object assembly and coding. Analyses of covariance were performed to compare neurocognitive measures, Δ FA and patient demographic factors between the three disease groups. Pearson's correlation analyses were performed to determine the relationships between neurocognitive measures, Δ FA and risk factors; age at treatment and irradiation dose, followed by multiple linear regression analysis to study the simultaneous influence of these factors on Δ FA.

Results:

DTI was performed in 28 of 30 patients. Patient demographics, mean Δ FA and IQ scores of three disease groups are summarized in Table 1. Only interval since treatment was significantly different between disease groups ($p = 0.032$). Pearson's correlation showed significant correlations between Δ FA and FSIQ (Fig. 1), VIQ (Fig. 2) and PIQ (Fig. 3) and irradiation dose ($r = -0.461$, $p = 0.047$). All three IQ scores remained independent variables influencing Δ FA after correcting for irradiation dose.

Tumor type	Δ FA (%) Mean (SD)	Age at MR (yr) Mean (SD)	Age at Rx (yr) Mean (SD)	Interval (yr) Mean (SD)	FSIQ Mean (SD)	VIQ Mean (SD)	PIQ Mean (SD)
ALL – RT	1.25 (2.82)	12.72 (3.86)	5.86 (5.82)	6.87 (4.07)	109.3 (18.6)	114.9 (18.6)	100.0 (16.0)
ALL + RT	0.80 (3.80)	13.79 (3.68)	6.71 (4.76)	7.33 (3.97)	107.3 (14.0)	109.3 (14.1)	103.7 (14.1)
MED	–3.76 (6.39)	11.01 (4.48)	8.62 (4.13)	2.39 (1.83)	102.4 (18.7)	107.9 (15.6)	95.8 (20.7)

Table 1 showing patient demographics, Δ FA and IQ scores of ALL patients without RT (–RT), with RT (+RT) and MED patients. Rx=treatment

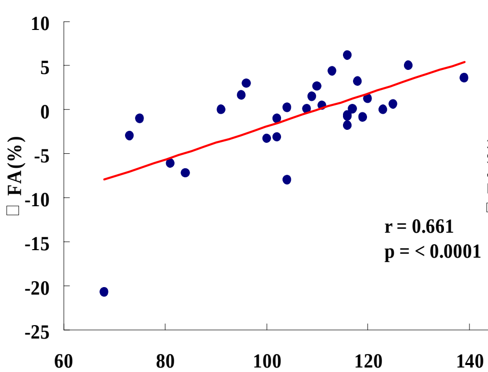

Fig. 1

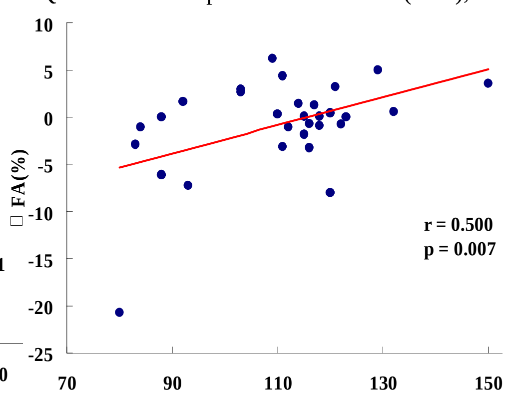

Fig. 2

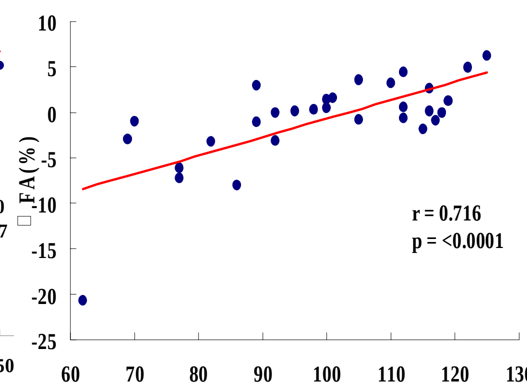

Fig. 3

Conclusion:

There is good correlation between severity of FA reduction and IQ scores, suggesting that white matter FA is a useful biomarker of treatment-induced neurotoxicity and may be used for the assessment and follow up of these patients.

References: 1. Leung LHT et al, *NeuroImage* 2004;21:261-268. 2. Khong PL et al, *Radiology* 2005 (in press)