Investigation of Long-Term Neurotoxicity of Irradiation and Chemotherapy by Diffusion Tensor Imaging and H-1 MR Spectroscopy in Children With Medulloblastoma and Pilocytic Astrocytoma

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Introduction: Neurologic and neuropsychologic deficits in long-term survivors of pediatric posterior fossa tumor are common sequelae of disease and therapy. In general, deficits in medulloblastoma (MB) patients are more pronounced than in patients who are diagnosed with pilocytic astrocytoma (PA). MB patients are treated with multimodal therapy including surgery, chemotherapy (vincristin, cisplatin, CCNU, intrathecal methotrexate) and whole-brain irradiation (24 Gy, infratentorial boost of 54 Gy), while PA patients undergo surgery only. The goal of our study was to measure the concomitant side-effects of irradiation and chemotherapy by comparing these otherwise similar two groups of patients. We hypothesized that neurotoxicity would be reflected by alteration of white matter as detected by diffusion tensor imaging (DTI) and quantitative H-1 MR spectroscopy (MRS). In a previous study MB patients were shown to suffer a significant decrease in fractional anisotropy correlating with inferior neurocognitive function when compared with healthy subjects.[1] Therefore, we undertook to measure correlates of parenchymal integrity by T2-weighted MR signal alterations, fractional anisotropy (FA), and metabolite concentrations in a prospective comparative study.

Patients and Methods: This study was approved by the institutional ethics committee and prior written informed consent of parents was obtained. 14 MB (age range 5-23y) and 14 PA patients (age range 5-20y) have been included in this on-going study to date. Patients were examined at their regular control periods, while post-therapeutic time ranged from 1y to 8y (median: 3 y, 2.5 m). MRI, DTI, and MRS were performed using a 3T-MR system equipped with an 8-channel headcoil (3T Signa Excite, GE Healthcare). The MRI protocol including interleaved T2-weighted fast spin-echo imaging (3 mm sections), contrast-enhanced T1-weighted IR-FSE imaging, and DTI (4 mm sections, 256 x 256 matrix) was accelerated using parallel imaging (no gap). FA maps were generated and analyzed using FUNCTOOL (GE Healthcare). Specific anatomic structures were assessed by selecting 17 standardized regions-of-interest (ROI) including the inferior (icp), medial (mcp), and superior (scp) cerebellar peduncles, crus cerebri (cc), anterior and posterior internal capsules (aic, pic), anterior and posterior commissures (ac, pc), supraventricular white matter (svWM), and the corona radiata (cr). The mean±SD of FA values of all voxels within one ROI was calculated.

MRS was performed in parietal white matter by selecting volumes-of-interest (VOI) of 4 ml and in midline parietal gray matter (GM) of 8 ml using the PRESS technique (TR/TE/NEX = 6000ms/30ms/64). Quantification of the resonances of creatine and phosphocreatine (Cre), N-acetylaspartate and N-acetylaspartylglutamate (tNAA), *myo*-inositol (mI), choline-containing compounds (Cho), and glutamate (Glu). was done with use of the operator-independent LCModel method.

Fig 1. Fractional anisotropy in WM
left: inferior cerebellar peduncle (icp)
mid: crus cerebri (cc)
right: anterior, posterior internal capsule (aic, pic)

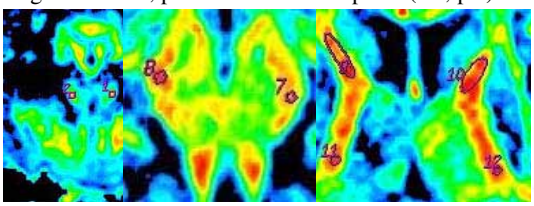
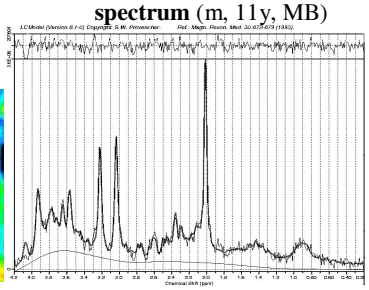
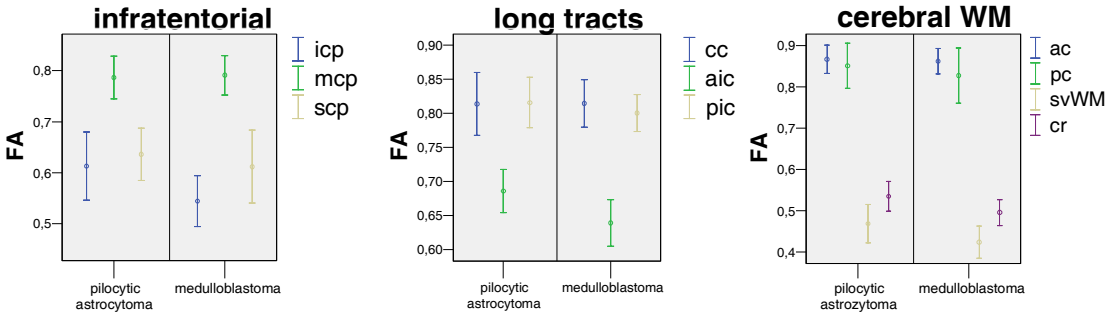


Fig 2. LCModel output of WM spectrum (m, 11y, MB)



Results: Compared with the PA cohort the FA of aic in MB patients was significantly decreased (Mann-Whitney-U-test, p=0.039). In the MB cohort a trend to lower values did not reach significance in cr (p=0.067) and svWM (p=0.14). Moreover, concentrations of tNAA and Cre in WM were decreased in both groups, while an increase of Glu was noted. Concentration differences between both patient groups were not significant in WM (Cre, p=0.1; tNAA, p=0.3; Glu, p=0.1) and in GM.

Fig 3. Fractional anisotropy of WM structures, mean and 95% confidence interval



Discussion: Differences in FA between small numbers of MB patients (n=9-12) and control subjects in prior studies[1] were more pronounced than differences between MB and PA patients in our study. Contrary to expectations, our observation of comparable FA in both patient groups should be due to surgical and neuroaxonal pre-treatment damage by the tumor itself, while the effect of irradiation in MB patients lead to minor changes that need larger patient numbers to let the trend towards lower values become statistically visible. The time between therapy and assessment as well as patient age had a large range and should be sorted out as a confounder. These findings encourage us to extend our study to larger numbers, to include proper age-matched normal controls and voxel-based morphometry for the assessment of FA.

Conclusion: Our preliminary data indicate that the long-term effect of irradiation in pediatric tumor patients may have been overstated and appears to be of secondary importance compared with the neurotoxic effects of the tumor proper and surgery.

References: [1] Khong, PL et al. "Diffusion-tensor imaging for the detection and quantification of treatment-induced white matter injury in children with medulloblastoma: a pilot study." Am J Neuroradiol 2003; 24:734-40.