Glutamate/glutamine complex, myoinositol and lipid in late radiation-induced injury of the brain: an in vivo 1H MRS study

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BACKGROUND and OBJECTIVES

Nasopharyngeal carcinoma is an example of an extra-cranial tumor for which radiation therapy frequently involves incidental irradiation of part of the normal brain. Radiation (RT)-induced temporal lobe necrosis in these patients provides the opportunity of an *in vivo* model to study the effect of late radiation-induced injury of the normal human brain without the confounding effect of tumor infiltration or its secondary effect. Using long TE ^{1}H MRS, we have previously shown a decrease of N-Acetyl-aspartate in these lesions and the presence of lactate in severe lesions [1]. Changes in lipid and Glutamine/Glutamate complexes (Glx) have been demonstrated in RT-induced cerebral injury in animals. We aimed to study Glx, myoinositol (mI), and lipid on short TE ^{1}H MRS in this unique group of patients.

MATERIALS AND METHODS

Forty-six patients who had nasopharyngeal carcinoma treated with standard RT plans at a radiation dose equivalent to at least 66 Gy complicated with RT-induced injury to the temporal lobes were recruited. MR imaging and ^{1}H-MRS were performed with a 1.5-T system. Single voxel ^{1}H-MRS of $2 \times 2 \times 2.5$ cm^3 volume at both temporal lobes was performed employing the point-resolved spectroscopy sequence using a TR 2000 ms and TE 30 ms. Data were acquired at a spectral bandwidth of 2,000 Hz, and 64 signals were averaged for each water-suppressed spectrum. Spectral analysis was performed with the fitting routine LCModel [2].The Glx resonances at 2.1-2.5 ppm and 3.75 ppm were both accounted for in Glx measurement in the LCModel. The presence of metabolite peak at 1.3-1.33 ppm representative of Lac/methylene resonance of lipid and methyl resonance of lipid at 0.9 ppm respectively was assessed qualitatively. Morphological lesion severity was graded on coronal T2-weighted and contrast-enhanced T1-weighted images and classified according to white matter (WM) lesion extent as no, minimal, mild, moderate, or severe (i.e. grades 0 -4) and according to the degree of mass effect as no, mild, moderate or severe (i.e. grades 0-3).

RESULTS

Satisfactory spectra were obtained in 43 temporal lobes with lesion and 9 morphologically lesion-free temporal lobes, in 36 patients. An example of T2-weighted image fFig.1a) and ^{1}H MRS spectra in a patient with right temporal lobe lesion of severe extent Fig.1b) and left temporal lobe lesion of minimal extent (Fig.1c) is given below. A significantly (p=0.002) higher Glx/Cr (mean 3.46, S.D. 2.54) was shown in temporal lobes with lesion (n=42) compared to the 9 lobes without morphological lesion (mean 1.67, S.D. 1.14) on MRI. A significantly (p=0.008) higher Glx/Cr (mean 4.13, S.D. 3.01) was shown in temporal lobe lesions showing mass effect (n=24) compared to the 28 lobes without mass effect (mean 2.25, S.D. 1.32). A significantly (p=0.016) lower mI/Cr (mean 0.63, S.D.0.48) was shown in temporal lobe lesions with mass effect compared to those without mass effect (mean 0.94, S.D. 0.39). Lac/Lipid peak was detected in 10 temporal lobes. Of 12 lobes with severe lesions, six had lipid peak detected. Glx/Cr showed an increasing trend with increasingly severe in WM lesion extent and increasingly severe mass effect (Figs 2 a, b.). There was a general decreasing trend of mI/Cr with increasingly severe mass effect except for the most severe grade (Figs. 3 a,b).

Fig. 1a Coronal T2-W image with voxels shown by white boxes

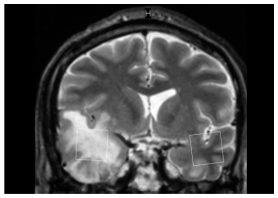


Fig.1b Spectra of severe lesion in right temporal lobe

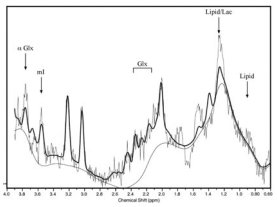


Fig.1c Spectra of mild lesion in left temporal lobe

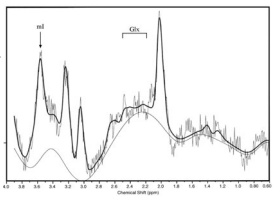


Fig 2a

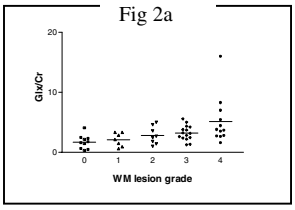


Fig. 2b

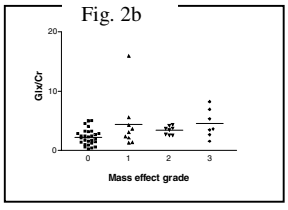


Fig. 3a

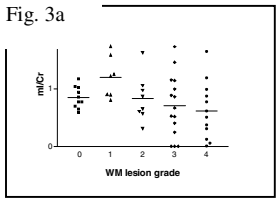
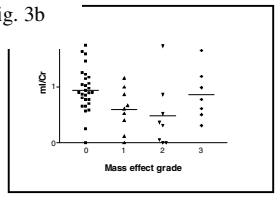


Fig. 3b



DISCUSSION

Elevation of Glx has been demonstrated in RT-induced cerebral injury in non-consistent manners in cats up to 9 months after irradiation with 50 Gy on short TE ^{1}H MRS [3]. In the current *in vivo* study, Glx/Cr was found to be increasingly elevated in patients with increasing grades of severity in white matter extent and mass effect in RT-induced temporal lobe injury. Glx elevation has been demonstrated during hypoxia and-ischemia. The Glx/Cr elevation may relate to the vascular injury theory whereby irradiation was thought to impose damage to the endothelial cells resulting in thrombosis or occlusion of small vessels and capillaries and interference of the normal blood perfusion. Alternatively it may be the result of ischemia arising secondarily by the increased tissue pressure from edema as a result of endothelial leak and blood-brain barrier disruption.

Myoinositol is a cerebral osmolyte with its uptake and release regulated in astrocytes by osmolarity changes. Myoinositol loss may also be explained by glial cell swelling accompanying tissue edema. Decrease in mI may also relate to hypoxia-ischemia as has been shown in secondary hypoxic encephalopathy [4].

Ten of the 52 satisfactory spectra in the irradiated temporal lobes showed the presence of lipid with resonances detected at both 1.3 and 0.9 ppm, confirming the presence of lipid. These occurred predominantly in temporal lobes with severe radiation -induced changes, which is in keeping with previous observations of lipid in irradiated animals and patients [5] and the higher lipid resonances in larger necrosis in astrocytomas *in vitro* [6].

CONCLUSION

Decrease of mI/Cr and increase of Glx/Cr was found in RT-induced brain injury and the changes generally correlated with morphological severity. Lipid was also more frequently found in severe lesions. The metabolite changes seem to reflect an underlying ischemic process which may be accompanied by osmolarity changes.

REFERENCES

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