

In vivo measurement of glutathione (GSH) in the human brain with secondary progressive multiple sclerosis using selective multiple quantum chemical shift imaging of GSH

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INTRODUCTION

Multiple sclerosis (MS) has long been identified as a chronic inflammatory demyelinating disease of the central nervous system [1 and refs therein]. Among many proposed mechanisms, oxidative stress has been implicated in the pathogenesis of multiple sclerosis (MS). Glutathione (GSH), a powerful antioxidant, plays a key role in the first line of antioxidant defense against free radicals and a reduction in GSH levels indicates the presence of oxidative stress in the brain. Patients with secondary progressive MS (SPMS) often worsens despite a stable T_2 lesion burden in MRI. Increased oxidative stress in the absence of measurable inflammation could explain this phenomenon. The objective of this study was to determine the levels of GSH in brains of the SPMS patients compared with those in normal controls and to investigate the potential role of cerebral GSH levels as a sensitive indicator of increased susceptibility to oxidative damage in MS.

METHODS

Seventeen SPMS patients (51 ± 8 years, mean \pm SD) and seventeen closely age- and gender-matched healthy controls (51 ± 8 years, mean \pm SD) were studied. The SPMS patients were selected based on their definite diagnosis of MS with a previous relapsing history and a gradual worsening of their function over at least 1 year. All experiments were performed on a Siemens Allegra 3 T MR system with a custom-built helmet RF coil and interface [2]. For the selective MQ CSI of GSH, a double-band frequency selective 180° pulse was used during MQ preparation period to ensure spectral selectivity for the strongly coupled cysteine protons of GSH at 4.56 ppm and 2.95 ppm [3]. GSH CSI was performed with 8×8 phase encoding steps, FOV of $20 \text{ cm} \times 20 \text{ cm}$, and slice thickness of 3 cm. The nominal voxel size of GSH CSI is $2.5 \text{ cm} \times 2.5 \text{ cm} \times 3 \text{ cm}$ without zero-filling. The CSI slice was positioned to across the frontal to parietal regions in the axial slices of the human brain *in vivo*. The brain regions were divided into “mainly frontal” and “mainly parietal” or “fronto-parietal” region that is the combined regions of the two. GSH concentration was determined from the regions of interest based on the internal reference method using the simultaneously measured creatine signal as an internal concentration reference [4].

RESULTS AND DISCUSSION

Figure 1 shows a partial view of GSH CSI from the brain of an SPMS patient. GSH signals of the cysteine β -CH₂ protons at ~ 3 ppm were clearly detectable in all the CSI voxels. GSH levels in the fronto-parietal region were 12.5% lower ($p < 0.004$) in the SPMS patients ($1.04 \pm 0.13 \mu\text{mol/g}$, mean \pm SD, $n = 17$) compared with those in the healthy controls ($1.04 \pm 0.13 \mu\text{mol/g}$, mean \pm SD, $n = 17$). The differences in GSH levels between two groups were 18.5% ($p = 0.001$) in the mainly frontal region and only $\sim 8\%$ in the mainly parietal region.

In this pilot study, we have demonstrated that GSH can be accurately measured in the brains of SPMS patients. Despite the small number of patients, we were able to demonstrate that GSH levels are markedly reduced in the brains of SPMS patients as compared to healthy controls. This reduction is most prominent in the frontal areas. The lower levels of GSH indicate that oxidative stress is an ongoing process in these patients. This could partially explain the ongoing functional decline in patients with SPMS in the absence of inflammatory activity by MRI. The capacity of assessing GSH levels in MS patients could provide a useful clinical tool to measure the effectiveness of medications that alter oxidative stress in the living patient.

REFERENCES

1. Frischer et al. *Brain* **132**: 1175 (2009). 2. Choi et al. *MRE* **31B**: 71 (2007). 3. Choi et al. *PISMRM* 521 (2003). 4. Choi et al. *MRM* **51**: 1115 (2004)

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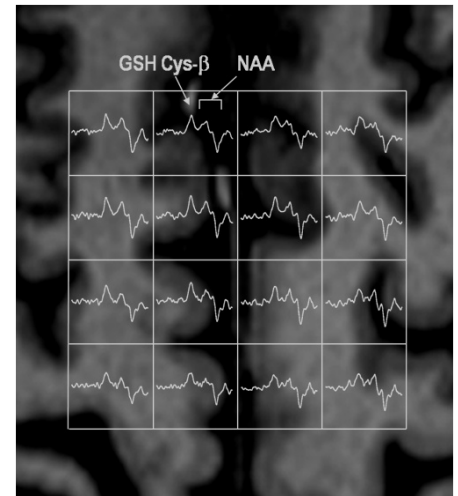


Fig. 1 Partial view of *in vivo* GSH CSI is overlaid on T1-weighted MRI of an SPMS patient at 3 Tesla (FOV = $20 \text{ cm} \times 20 \text{ cm}$, slice thickness = 3 cm, 8×8 phase encoding step and nominal voxel size = 4.7 ml , 1 x zero filling).