

## Increased frontal glutamine in patients with idiopathic generalised epilepsy using MEGAPRESS spectroscopy

Fahmida A Chowdhury<sup>1</sup>, Ruth L O'Gorman<sup>2</sup>, Jonathan O'Muirheartaigh<sup>1</sup>, Mark P Richardson<sup>1</sup>, and Gareth J Barker<sup>3</sup>

<sup>1</sup>Department of Clinical Neuroscience, Institute of Psychiatry, KCL, London, United Kingdom, <sup>2</sup>Center for MR Research, University Children's Hospital, Zurich, Switzerland, <sup>3</sup>Department of Neuroimaging, Institute of Psychiatry, KCL, London, United Kingdom

### Background

Most previous spectroscopic studies in epilepsy have reported Glx levels, which represent a combined measure of Glu (glutamate), the major excitatory neurotransmitter, and Gln (glutamine), the metabolic counterpart of glutamate. Previous studies using magnetic resonance spectroscopy in patients with idiopathic generalised epilepsies (IGE) have reported increased Glx and reduced N-acetyl aspartate (NAA), in frontal and thalamic regions<sup>1,2,3,4</sup> with conflicting reports of both raised and reduced GABA<sup>5</sup>. Glu and Gln have overlapping peaks that are difficult to separate and their metabolism is tightly coupled. After neuronal release of glutamate, its action in the synaptic cleft is terminated by glial uptake of glutamate via excitatory amino acid transporters (EAATs). In glial cells, glutamate is converted into glutamine by the enzyme glutamine synthetase. The inactive glutamine is then transferred back to the neurone where it is reconverted to glutamate and stored in synaptic vesicles. Since there are significant amounts of intracellular glutamate which do not take part in synaptic transmission, it has been suggested that glutamine is useful surrogate marker for synaptically active glutamate. Recently MEGAPRESS spectroscopy has been used for quantification of GABA and it has been shown that the MEGAPRESS acquisition also allows detection of glutamine with greater sensitivity than that of the PRESS acquisition<sup>7</sup>.

### Objectives

In this study we sought to identify whether patients with idiopathic generalised epilepsy had increased Gln and altered GABA levels compared with control subjects.

### Methods

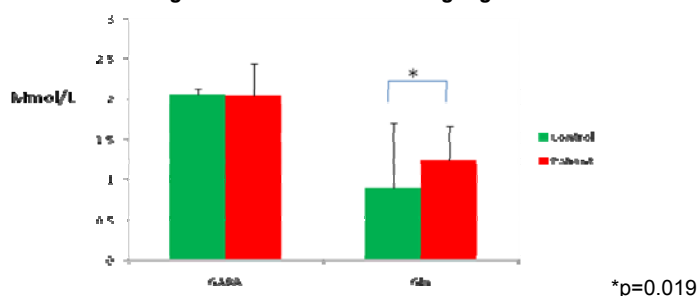
**Subjects:** 13 patients with IGE and 15 controls were scanned using a 3 Tesla GE HDx system (General Electric, Milwaukee, WI). **Image acquisition:** A 3-dimensional isotropic high resolution inversion recovery prepared spoiled gradient-recalled echo (JIR-SPGR) scan was obtained in the axial plane FOV 28 cm<sup>2</sup>, Matrix size 256x256, 124 partitions, giving an isotropic voxel size of 1.1mm<sup>3</sup>, TE = 2.8ms, TR = 7 ms, inversion time = 450ms, flip angle = 20°. The SPGR images were used to prescribe a voxel of 25 x 40 x 30mm<sup>3</sup> in the left dorsolateral prefrontal cortex (DLPFC), 1.5mm above the superior margin of the lateral ventricles on the axial image, a third along the length of the interhemispheric fissure and halfway along width of the left hemisphere. Spectra were acquired using the MEGAPRESS method<sup>8</sup> (T<sub>E</sub>=68, T<sub>R</sub> =1800, with 160 edited/ unedited pairs). **Image processing:** The MEGAPRESS data were processed with LCModel 6.1-4F using a simulated basis set<sup>9</sup>. For GABA quantification, the baseline was constrained to prevent the mis-assignment of the GABA peak to the baseline; Glutamine values were calculated without a constrained baseline, to avoid underestimation of Gln. Metabolite concentrations were corrected for the voxel CSF content, since CSF is considered to provide negligible contribution to the Gln and GABA signals. **Statistical analysis:** ANOVA was used to investigate group differences between the two groups with age entered as a covariate. In order to correct for multiple comparisons, a Bonferroni correction factor of 2 was applied (p <0.025 considered significant).

### Results

**Table 1: Metabolite concentrations expressed as group mean (SD) for controls and patients with IGE**

Metabolite	Control	Patient
GABA mmol/L	2.06 (0.080)	2.05(0.82)
Gln mmol/L	0.89(0.39)	1.25(0.42)

**Figure 1: Bar plots showing metabolite values for controls (green) and patients (red). Error bars show standard deviations and significant differences are highlighted with stars.**



### Discussion

The data presented here support the hypothesis that patients with IGE have increased frontal glutamine compared with controls, which is consistent with previous studies that report increased Glx (Gln + Glu) in similar groups of patients. However, since Gln has been suggested to act as a surrogate for metabolically active glutamate<sup>6</sup>, it may represent a more sensitive measure for excitatory neurotransmission than Glx. The lack of a significant difference in GABA may be due medication status.

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