Association between cortical lesions and GABA concentration in progressive multiple sclerosis.

Maria Petracca, MD[1,4]; Kornelius Podranski, M.Sc.[1]; Lazar Fleysher, PhD[1]; Sirio Cocozza, MD[5]
Fred Lublin, MD[1]; Malgorzata Marianska[6]; Matilde Inglese, MD, PhD[1,2,3,7]

[1]Dep. of Neurology, [2]Radiology and [3]Neuroscience, Icahn School of Medicine at Mount Sinai, New York, USA; [4]Dep. of Neurosciences, University of Naples "Federico II", Naples, Italy; [5]Dep. of Advanced Biomedical Sciences, University of Naples "Federico II", Naples, Italy; [6]Center for Magnetic Resonance Research and Department of Radiology, University of Minnesota, Minneapolis, Minnesota, USA; [7]Institute of Mental Health Research, University of Ottawa, Ottawa, Canada; [8]Department of Neuroscience, University of Genoa, Genoa, Italy.

Background

Gamma-aminobutyric acid (GABA) is the principle inhibitory neurotransmitter in the brain. Reduced GABA levels are associated with disability in progressive multiple sclerosis (MS) and reflect pathological abnormalities that may include decreases in the pre- and postsynaptic components of GABA neurotransmission and in the density of inhibitory neurons (Cawley et al., 2015). In addition to grey matter (GM) atrophy, cortical lesions (CLs), which are know to occurr with high prevalence in progressive MS (Calabrese et al. 2009) and to correlate with both cognitive and physical disability (Petracca et al., 2017; Calabrese et al., 2012), might be a relevant structural substrate of GABA concentration reduction.

Aim

To investigate the pathological abnormalities that underlie GABA decrease in progressive MS, focusing on the possible role of CLs.

Methods

Population

Thirty-one progressive MS patients (11 men, mean age 53.1±9.1 years) were enrolled along with 26 healthy controls (HCs) of comparable age and sex (15 men, mean age 50.0±7.6 years).

Acquisition

The following protocol was acquired with a 3T MRI scanner (MAGNETOM Skyra, Siemens, Erlangen, Germany) using a 32-channel head coil: T1-weighted sequence (sagittal MPRAGE, TR: 3000 ms, TE: 2.47 ms, TI: 1000 ms, Flip Angle: 7°, Turbo Factor: 224, FOV: 256mm, Slice Thickness: 0.80 mm, Number of Slices: 224, Base Resolution: 320, Image Area: 256x256x180 mm³), T2-weighted sequence (axial TSE, TR: 8000 ms, TE: 95.0 ms, Flip Angle: 160°, Turbo Factor: 11, FOV: 256mm, Slice Thickness: 3.00 mm, Number of Slices: 54, Base Resolution: 256, Image Area: 350x263x350 mm³); axial double inversion recovery-DIR (TR: 7500ms, TE:131ms, TI: 3000ms, voxel-size: 0.5x0.5x3mm).

MRS data were acquire using a MEGA-PRESS sequence (Marjanska et al., 2013), (TR 2.6 s, TE: 68 ms) with double-banded editing pulses (180° Shinnar-Le Roux; duration, 17 ms; bandwidth, 70 Hz). Spatial localization in PRESS was performed using a 90° Hamming-filtered sinc pulse (duration: 2.12 ms; bandwidth: 4.2 kHz) and two 180° mao pulses (duration: 5.25 ms; bandwidth: 1.2 kHz). Additional water suppression using variable power with optimized relaxation delays (VAPOR) and outer volume suppression techniques was added prior to MEGA-PRESS.

The final spectra were obtained by subtracting spectra acquired with the double-banded editing pulse applied at 1.9 and 4.7 ppm (EDIT ON) from those acquired with the double-banded editing pulse applied at 4.7 and 7.5 ppm (EDIT OFF). 128 pairs of water suppressed and one pair of water unsuppressed spectra where obtained.

Vendor provided semi-automatic shimming procedure resulting in line-width below 8 Hz was performed prior to the spectroscopic acquisition.

Volume of interest (VOI) was placed at the level of the left sensorimotor cortex using the hand knob as reference (Fig.1).

Spectral processing

The 128 EDIT ON and 128 EDIT OFF spectra as well as the water unsuppressed average were pre-processed using in-house MATLAB (The MathWorks, Inc., Natick, MA) scripts adopted from (Marjanska et al., 2013). The software routine corrected the individual free induction decays for Eddy-Currents as well as fequency- and phase-shifts using the Creatine peak at 3.03 ppm. Difference spectra were afterwards generated by subtracting each EDIT ON/EDIT OFF pair.

Spectra were analysed using LCModel 6.3-1J together with a base-set specifically created in (Marjanska et al., 2013). Based on the recommandation from LCModel manual the range of 0.50 ppm to 1.20 ppm and 1.95 to 4.5 ppm was analyzed. The gap from 1.20 ppm to 1.95 ppm was introduced to account for artifacts visible in some of the datasets. Quantification of metabolites (NAA, GABA, GLX) was performed using an unsuppressed water signal obtained from the same MRS voxel.

Concentrations reported by LCModel were corrected for cerebrospinal fluid, T1 and T2 relaxation times. MRI-visible water density of GM, WM and CSF was assumed to be 0.78, 0.65, and 0.97. Tissue fractions of the MRS voxel were calculated in MATLAB by overlaying the MRS VOI onto the tissue masks obtained by SPM12 (http://www.fil.ion.ucl.ac.uk/spm) segmentation of the T1 image.

Average ± SD water line width obtained was 5.1±1.2 Hz. 17. SNR ± SD was 58.8 ± 5.4. Cramér-Rao lower bounds were lower or equal to 18%.

CLs assessment

Cortical lesions number inside the VOI was recorded for each patients evaluating Double Inversion Recovery (DIR) images (Fig.2)

Statistical analysis

Differences between MS patients and HC in terms of GABA concentrations were tested via GLM, taking into account for effect of age and gender, while correlations with CLs count were probed with the Pearson correlation coefficient.

Results

MS patients showed lower GABA concentrations in the left sensorimotor area compared to HC (1.52±0.21 vs 1.67±0.16 respectively, p=0.009).

Ten out of thirty-one MS patients presented CLs within the VOI, with a mean number of 1.5 CLs in the sensorimotor area. HC did not show any cortical pathology on DIR images.

When evaluating possible correlations between GABA concentrations and number of CLs, a significant inverse correlation emerged (r=-0.652, p=0.041).

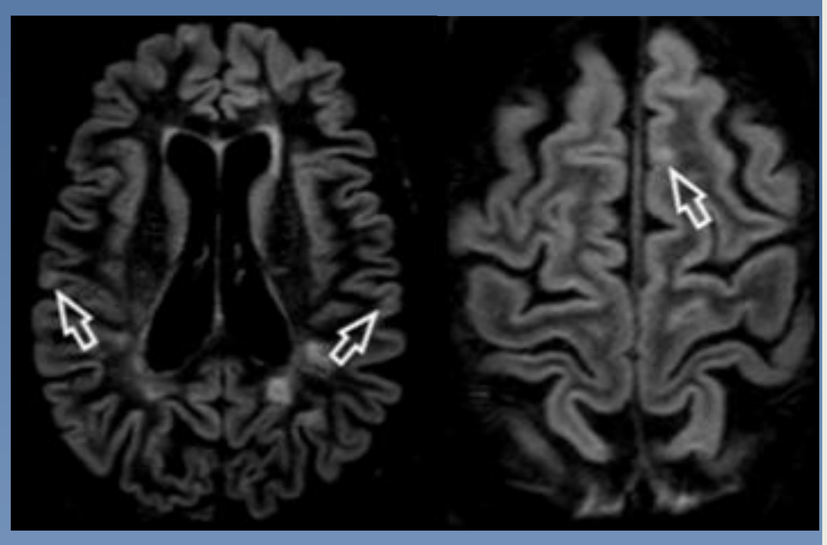

Fig.2 Axial DIR MR images of the brain in a patient with primary progressive MS demonstrating focal lesions in the cortical grey matter (arrows).

Conclusions

The reduction of GABA concentration observed in progressive MS seems to be partially accounted for by the presence of CLs. Further analyses on the role of cortical atrophy and white matter lesions are currently ongoing.

Acknowledgements

This study was supported in part by National Multiple Sclerosis Society (NMSS RG 5120A3/1).

References

Calabrese et al. Cortical lesions in primary progressive multiple sclerosis: a 2-year longitudinal MR study. Neurology 2009; 72, 1330–6.

Calabrese et al. Cortical lesion load associates with progression of disability in multiple sclerosis. Brain.2012 ;135:2952-61.

Cawley et al. Reduced gamma-aminobutyric acid concentration is associated with physical disability in progressive multiple sclerosis. Brain. 2015 Sep;138:2584-95.

Petracca et al. Synchronization and variability imbalance underlie cognitive impairment in primary-progressive multiple sclerosis. Sci Rep. 2017. doi: 10.1038/srep46411.

Marjanska et al. Brain Dynamic Neurochemical Changes In Dystonic Patients: A Magnetic Resonance Spectroscopy Study. Movement Disorders 2013;28(2):201-209.

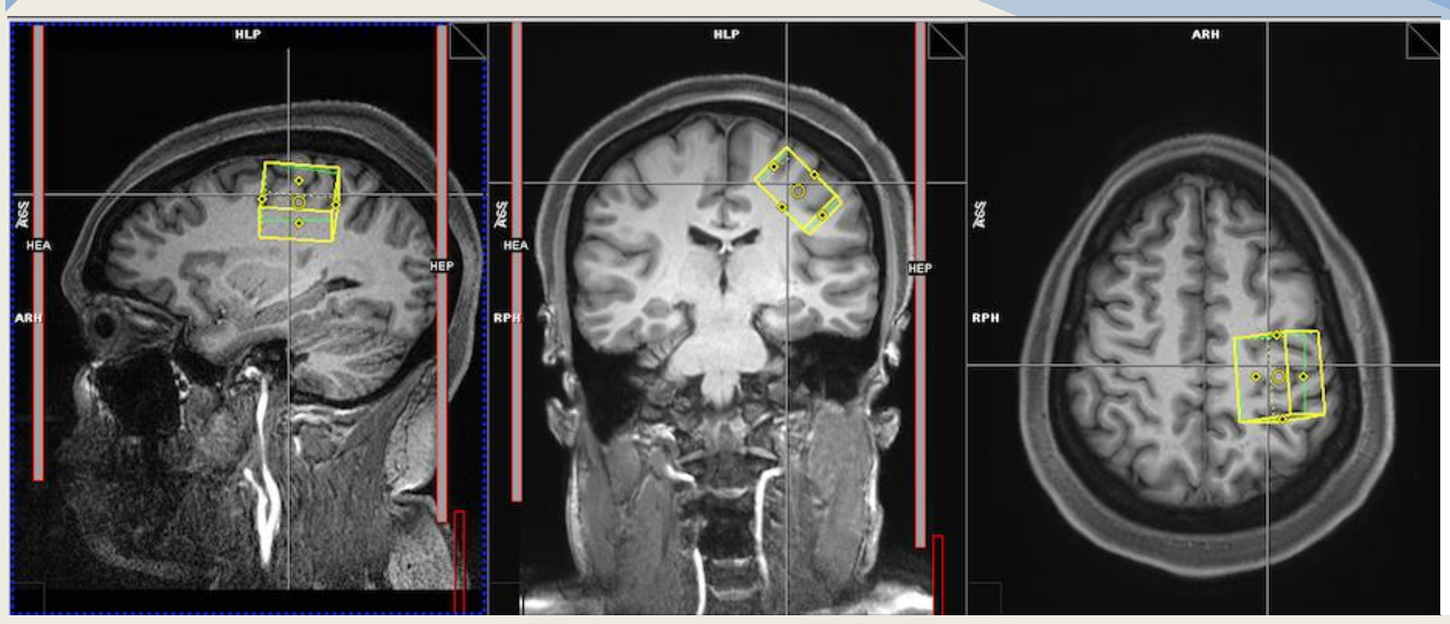

Fig.1 Examples of the MR spectrum. Placement of magnetic resonance spectroscopy voxel (left) with its example magnetic resonance spectroscopy spectrum (right) in the sensorimotor cortex.