Combined 31P and 1H-MRS Study on Brain Energy Metabolism in Progressive Supranuclear Palsy (PSP)

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Introduction

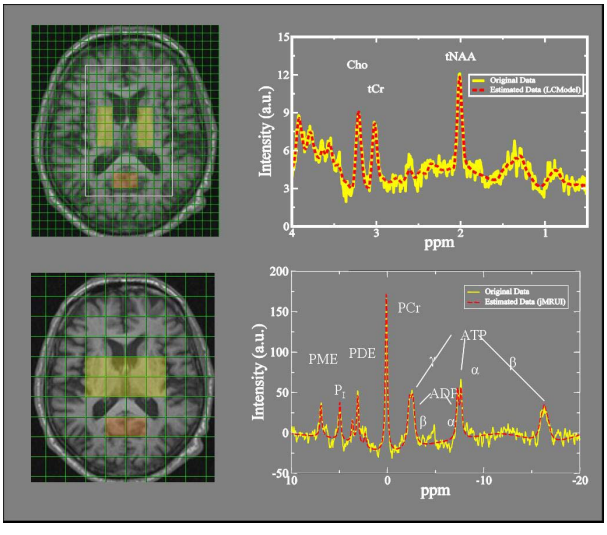
Progressive Supranuclear Palsy (PSP) is a sporadic neurodegenerative disorder with an average annual incidence of 5.3 per 100000, (1). Clinically, PSP results in a Parkinson syndrome with prominent postural instability, oculomotor deficits, and cognitive decline (for review: (1, 2)). The progression of PSP is rapid and the median survival after onset of symptoms is 5-10 years. Experimental evidence suggests that mitochondrial dysfunction, particularly complex I inhibition, may contribute crucially to the etiology of PSP. Presently, there is no known effective symptomatic or neuroprotective therapy for PSP, but coencyme Q10 (CoQ10) might be a means to improve cerebral energy metabolism, reduce cerebral free radicals and to ameliorate clinical symptoms in PSP (3, 4). *In vivo* MRS using either ^{31}P (5) or ^{1}H (6, 7) nuclei disclosed significant metabolic differences between patients and age-matched normal controls. This study was aimed at exploiting the full potential of combined ^{31}P and ^{1}H MRS to thoroughly specify parameters for energy metabolism and neuronal damage which can serve as markers for monitoring treatment with CoQ10.

Material and Methods

Patients: Eleven healthy controls (age 59.7±8.6 yrs) and 21 patients (age 66.2±6.3 yrs) with PSP staging system ≤ III, were included in the study. Patients underwent clinical tests of motor, cognitive, and behavioral functions. Controls were free of systemic, neurological, or psychiatric diseases.
MRS data acquisition: MRS of the brain was performed on a 3T whole body system (Magnetom Trio, Siemens Medical AG, Erlangen, Germany) with a double tuned ^{1}H/ ^{31}P volume head coil (Rapid Biomedical, Würzburg, Germany). For ^{1}H MRS, a 1.5 cm axial slice including the basal ganglia was recorded with 2D chemical shift imaging (CSI, circular phase encoding on a 16x16 matrix extrapolated to 32x32, 240 mm^2 FOV, TR 1500 ms, TE 30 ms). A 3D CSI sequence with WALZ4 proton decoupling was used for ^{31}P MRS. Circular phase encoding was employed with a weighted acquisition scheme on a 10x10x8 matrix extrapolated to 16x16x8 resulting in a series of axial slice with nominal 2.5 cm thickness and 17.5x17.5 mm^2 in plane resolution (flip angle 60°, TR 2000 ms, TE 2.3 ms). For both modalities, slice (slab) angulation and offsets were identical.
MRS data analysis: Data were exported from the scanner console and processed offline on a Linux workstation. Fig. 1 shows the respective slices for 1H and 31P. The nominal resolution is indicated by the grid, colored areas mark regions of interest used for data averaging. For quantitative analysis ^{1}H MRS spectra were fitted in the frequency domain by a linear combination of a set of model spectra (8) using LCModel. ^{31}P spectra were analysed in the time domain with the jMRUI software tool employing the non-linear least square fitting algorithm AMARES. The tissue pH was calculated according to Petroff et al. (9). Mg^{2+} was estimated as described by Iotti et al. (10). Absolute concentrations were calculated by referring to an independent phantom measurement. For ^{1}H MRS, T1 and T2 correction terms were applied as described in (11). No further corrections were applied for quantifying the ^{31}P data. Each complete CSI data set was screened for lactate: Spectra where visually inspected whether they exhibited a clear positive dublet signal at 1.3 ppm. Only those voxels were considered as lactate positive but no further attempt in quantification of was made.

Results and Discussion

No significant differences were detected for ^{1}H detectable metabolites total creatine (tCr) and N-acetylaspartate (tNAA). However, ^{31}P MRS showed a significant decrease of inorganic phosphate (Pi), phosphocreatine (PCr), and ATP in the basal ganglia (Fig.2) while in the occipital cortex only ATP was reduced. Lactate was never detected in controls but in approximately 20% of the patients. Calculation of ADP and the phosphorylation potential (PP) using standard equilibrium constant for creatine kinase (12) yielded no differences between patients and controls (Table 1). This indicates that reduced mitochondrial activity is compensated by reduction of ATP and inorganic phosphate leaving the PP constant, which may account for the rather mild decrease in tNAA. The decrease of phosphometabolites like ATP and Pi should be a marker of the severity of the disease and potential effects of treatment.



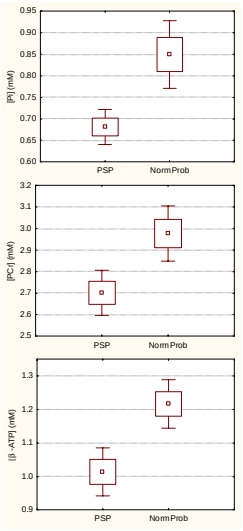


Fig.1: CSI slice, grid resolution and ROI selection for ^{1}H and ^{31}P MRS. Spectra show original (yellow) and fitted (red) data.
Fig.2: ^{31}P metabolite concentrations for basal ganglia (yellow marked ROI in Fig.1).

Table 1: ADP and phosphorylation potential calculated from ^{1}H and ^{31}P data:

	ADP mM^{-1}	ADP mM^{-1}	PP mM^{-1}	PP mM^{-1}
ROI	basal ganglia	occ. cortex	basal ganglia	occ. cortex
PSP patient	0.0131	0.0089	113	164
healthy volunteer	0.0139	0.0087	103	167

References

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