Decreased R2 and Increased Concentrations of Multiple Cerebral Metabolites in the Restless Legs Syndrome (RLS) brain: Exploring Iron Deficiency Consequence in RLS

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INTRODUCTION:

Restless legs syndrome (RLS) is a neurological disorder in which iron deficiency in the central nervous system is a contributing factor. The previous studies have demonstrated iron deficiency for RLS patients in the gray matter regions strongly coupled with the motor function of human body movement [1-2]. However, *in vivo* human studies which link iron deficiency to brain metabolism in RLS have not been previously reported. Thus, the aim of our study was to investigate the effect of insufficient iron contents in RLS on the neurochemical metabolism in the human brain, especially in the putamen, using *in vivo* MRI and proton MRS, respectively.

METHODS:

Subjects: 17 patients with RLS (mean age 52.7±13.8 yrs) and 18 age- and gender-matched healthy volunteers (mean age 48.3±17.5 yrs) were recruited in this study. RLS severity was evaluated using the International Restless Legs Syndrome Study Group (IRLSSG) rating scale after discontinuation of RLS medication for at least one week to eliminate drug effects.

MRI: Whole brain multi spin-echo images were acquired axially (TR=3.8s, 13 echoes, echo spacing=8ms, matrix=256×256, voxel size=0.9×0.9×4mm)

^{1}H MRS: T1-weighted image with high resolution (TR/TE=9.9ms/4.6ms, matrix size=256×256) was performed on a 3.0T system (Achieva, Philips) for the placement of a single voxel (1.5×1.5×1.5cm^3) in the putamen. Localization was achieved by a short echo PRESS (TR/TE= 2000/30ms, number of points=1024 and acquisition time=5 min). Water suppression was achieved with outer volume suppression.

Quantification: *In vivo* ^{1}H NMR spectra were analyzed using LCModel software [3]. Only metabolites that had a Cramer-Rao lower bound (CRLB) <20% were included in the analysis.

Statistics: Two-sample t-test was done for the group comparison using SPSS.

RESULTS:

The voxel-based MRI result showed that mean R_2 ($1/T_2$) values were decreased in gray and white matter regions in the RLS brain. (Figs 1-2). The MRS results showed a significant increase in various metabolites in the RLS patients compared to control subjects: Pho+Cho (tCho), NAA+NAAG (tNAA), NAA, glutamate(Glu), and mI (t-test, P<0.05).

DISCUSSION & CONCLUSION:

Contrary to previous reports, our study suggests that decreased iron concentrations in the RLS brain are more global findings. A significant increase was found in various metabolite concentrations in the RLS group. It is important to note that the NAA concentrations were increased in RLS. Since NAA is required for the production of myelin [4], increased NAA level may represent decreased utilization of the compound for myelination. Thus, the decreased total myelination of the brain may be consequence of insufficient iron concentration in the RLS brain. We may speculate that the observed increase in concentration of excitatory neurotransmitter glutamate suggests overall decreased glutamate transmission, resulting in its accumulation. The findings of our study may provide insight into neurochemical derangements resulting from iron deficiency in RLS. The reversibility with iron supplementation, as well as their effect on neuronal biochemical function, has yet to be studied.

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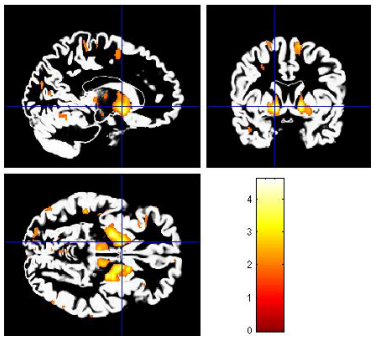

Fig. 1 Voxel-based comparison on R_2 maps showing significant R_2 decreases in the subcortical gray matter in RLS. P<0.05

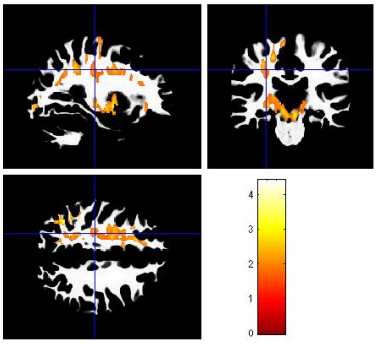

Fig. 2 Voxel-based results on R_2 maps showing significant decrease in R2 in white matter in RLS. P<0.05

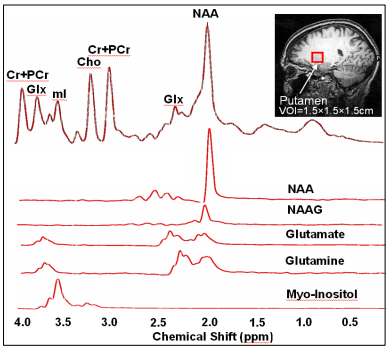

Fig. 3 ^{1}H-MRS-derived spectra in the putamen of a RLS patient.

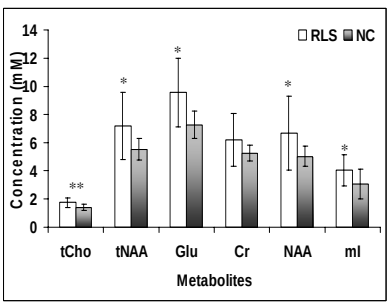

Fig. 4 The graph showing the comparison of metabolite concentrations. **P<0.002, *P<0.05