High-resolution ^{1}H NMR spectroscopy reveals differences in CSF metabolic profiles for MS patients with inflammatory vs. non-inflammatory plaques

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Introduction

Multiple sclerosis (MS) is a remarkably heterogeneous disease of the central nervous system (1). At present, numerous clinical and biomedical studies are being carried out to further characterize MS in its various forms and stages. Among other methods, ^{1}H NMR spectroscopy of cerebrospinal fluid (CSF) has been employed to detect differences in metabolic profiles beween MS patients and controls. Increased concentrations of lactate (lac) in CSF from MS patients have been reported by some authors (2), but not by others (3). No differences have been observed for relapsing-remitting (RR) vs. primary progressive (PP) MS (2). Lactate is considered to be a marker of acute inflammation, and increased lac/creatine *ratios* have been found in CSF of MS patients with inflammatory, gadolinium-DTPA contrast-enhanced plaques at brain MRI (4), vs. patients *without* contrast-enhanced (active) plaques. Therefore, it was hypothesized that these increased *ratios* may reflect an increased CSF content of lactate stemming from inflammatory plaques (4). We present here results of a study comparing true ("absolute") metabolite *concentrations* [mM] for CSF from patients with contrast-enhanced plaques (group 1) vs. patients *without* contrast-enhanced plaques (group 2).

Methods

CSF was obtained by lumbar puncture from 33 MS patients at the time of the first episode, before any treatment (clinically isolated syndrome, CIS). Twenty-one of these patients showed various amounts of contrast-enhanced plaques at MRI, while 12 patients showed non-enhanced plaques only. CSF was lyophilized and prepared in D_2O for NMR analysis as described elsewhere (5). NMR spectra were acquired at 28° C on an AVANCE 400 spectrometer (Bruker, Ettlingen) using full-relaxation conditions (TR=57.5 s, 90°-pulse with water suppression) and 64K data points. Metabolites were quantitated using trimethylsilyl tetradeuteropropionate (TSP-d4) as an internal standard. Statistical comparison of metabolite concentrations for groups 1 and 2 was performed using the non-parametric Mann-Whitney U test (Statview, Cary, NC).

Results

The metabolic profiles for groups 1 and 2 were very similar. Moderate but statistically significant differences were observed for one of 24 assigned metabolites (lac), and for one signal (1.08 ppm) from an unassigned compound, U (see doublet in Fig. 1 showing a typical CSF spectrum for a patient with inflammatory plaques; Table 1). Assignment of U is currently underway. Phenylalanine (phe) tended to be less concentrated in CSF from group 1 than in group 2, although this difference was not statistically significant ($p>0.05$).

Discussion

We were able to confirm the hypothesis that (molar) lactate *concentrations* are slightly increased in CSF from patients with inflammatory plaques vs. patients with non-inflammatory plaques only, at a verly early stage of the disease. Thus, conflicting reports with respect to differences in lac concentrations for MS vs. normal CSF may be rooted in the type of MS patients involved in each study, i.e. to what extent the group of MS patients investigated consisted of patients with active plaques. The corresponding explanation may also apply to phenylalanine (and the unassigned compound, U) since these metabolites were found to be slightly decreased (increased) for MS with inflammatory vs. non-inflammatory plaques, in analogy to results obtained for MS vs. normal CSF (2).

Figure 1

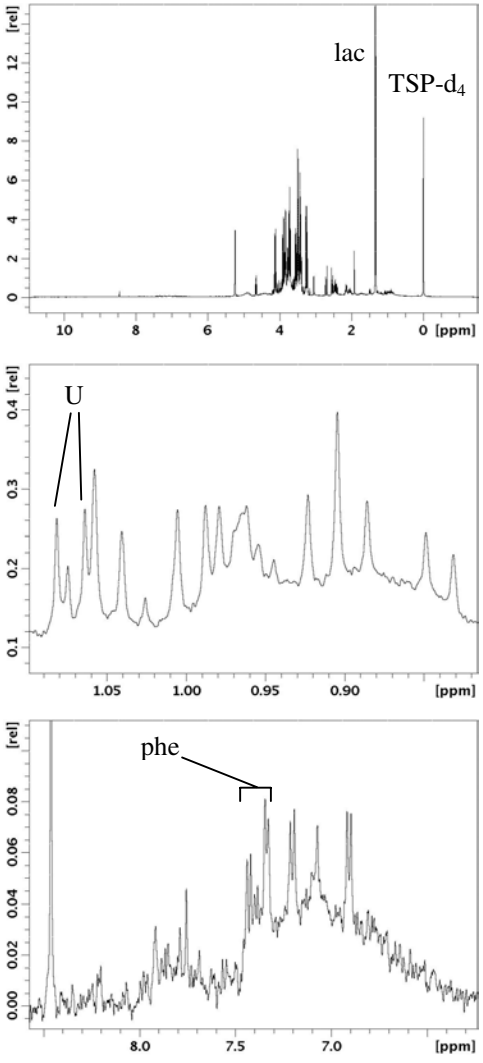

Table 1

	lactate	U	phenylalanine
	[mM]		[mM]
group 1 (inflammatory plaques)	2.44 ± 0.36	0.019 ± 0.004	0.012 ± 0.004
group 2 (no inflammatory plaques)	2.16 ± 0.29	0.015 ± 0.004	0.014 ± 0.003
p	0.0433	0.0213	0.1160

References (1) Brueck W et al, Curr Opin Neurol 18, 221-224 (2005); (2) Nicoli F et al, C R Acad Sci 319, 623-631 (1996); (3) Garseth AJ et al, Acta Neurol Scand 95, 9-12 (1997); (4) Simone IL et al, J Neurol Sci 144, 182-190 (1996); (5) Maillet S et al, Brain Res Brain Res Protoc. 3, 123-134 (1998).