MRI properties of cerebrospinal fluid for assessment in neurodegenerative diseases

Alexia Daoust[1], Stephen Dodd[1], Govind Nair[1], Steven Jacobson[1], Daniel S. Reich[1], and Alan Koretsky[1]
[1]*NINDS, LFMI, NIH, Bethesda, MD, United States*

INTRODUCTION There continues to be interest in using changes in CSF properties to image neurodegenerative diseases[1,2]. Due to the different relaxation properties of CSF and tissue there are many MRI sequences that enable segmentation of CSF from tissue[3-4]. Optimization of these sequences requires understanding CSF relaxometric properties. While T_1 and T_2 values in the brain tissue have been published, there is a poor literature about CSF relaxation times. In this study, we aimed to establish the values of T_1 and T_2 for *in vitro* human and monkey CSF, as well as protein solution at 14.1T and the T_2 for *in vivo* mice CSF at various field strengths. We aimed also to determine whether the T_1 and/or T_2 values show any changes according protein and metal CSF concentration.

METHODS ***IN VITRO Patients***: CSF was removed via a lumbar puncture from 4 HAM/TSP (HTLV-I-Associated Myelopathy/Tropical Spastic Paraparesis) 8 multiple sclerosis (MS) and 3 healthy patients (male and female, ~ 45 y.o.). **Animals**: CSF was removed via a transcutaneous cisterna magna puncture in 3 healthy monkeys (male and female, 10 y.o, rhesus macaque monkey). ***Phantoms***: solution of saline and bovine serum albumin (BSA, 10-200 mg/dL). ***MRI***: T_1 and T_2 values were calculated at 37°C on a 14.1 T MRI system (Bruker) using a volume transmit and receive coil. *T_1 Measurement:* Imaging was performed using a variable TR pulse sequence (RARE-VTR) with TE = 7.6 ms, TR = 500, 1163, 2016, 3213, 5243 and 15000 ms, slice thickness of 0.5 mm and an in-plane resolution of 0.3 mm^2. *T2 Measurement:* Spectroscopy was performed using a mutiecho CPMG sequence with TR = 20000 ms, TE = 1.875 – 1029 ms (intervals of 15 ms). ***Post-Processing:*** T_1 and T_2 map were calculated by performing a mono-exponential fit of the pixel or echo intensities. T_2 map was fitted using a non-negative least squares method[5] and the spectrums were analyzed. R1 and R2 values were plotted against the protein concentrations. To evaluate whether the R1 and R2 is a predictor of protein concentration, the p-value for Pearson's correlation coefficient (R^2) was computed. ***Protein quantification***: The CSF protein concentration was quantified according to the Bradford method[6]. ***Metals quantification***: The CSF metals quantification of Cu, Fe, Mn and Zn was performed by inductively coupled plasma mass spectrometry (ICP-MS, Exova, California) technique (500µL of each sample).

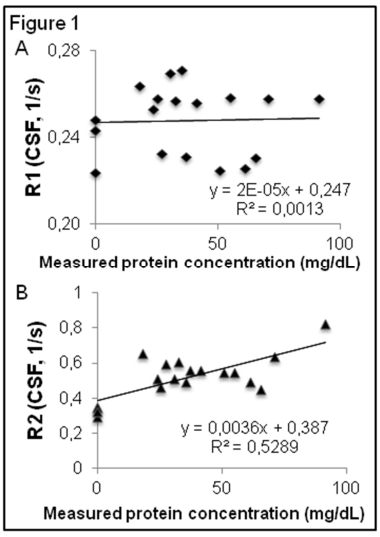
IN VIVO Animals: 12 healthy mice (C57Bl6 male, 3 m.o.) were used, n=3 per field. All procedures were performed under isoflurane anesthesia (2.5%). ***MRI***: T_2 was calculated on a 1, 4.7, 9.4 and 11.7T MRI system (Bruker). *T_2 Measurement:* see above. ***Post-Processing***: see above for the T_2 map calculation. T_2 values are expressed as mean ± Standard Deviation (Fig 2).

RESULTS *In vitro* T_1 of human and monkey CSF was close to that of saline (difference <6%), however, the differences in T_2 between saline and CSF were large (~ 40%; Table 1). CSF samples were from different diseases in order to have a large protein concentration range [18-92 mg/dL]. We observed a weak correlation (p=0.01) between R_2 of CSF and protein concentration for both human (Fig 1B) and monkey CSF (data not shown), which is not observed for the R_1 (Fig 1A). Interestingly, human and monkey CSF R_2 changing rate was longer than the one of BSA solutions (4.10^{-3}; 3.10^{-2} and 1.10^{-3} $mg/dL^{-1}/s^{-1}$, respectively) indicating that there is either a specific protein(s) or other constituents on CSF with high relaxivity. To test whether paramagnetic metals ions could explain the T_2 relaxivity of CSF, we calculated they concentration (Table 1). For all metals, the concentration was too low to modify significantly the CSF T_2 relaxivity. At 11.7T, the *in vivo* CSF T_2 (0.39 ± 0.01 s) was shorter than *in vitro* (Table 1). The Fig 2 shows a CSF T_2 decrease with an increase in field strength. *In vivo* and post mortem CSF T_2 diverges with increasing field strength.

Table 1

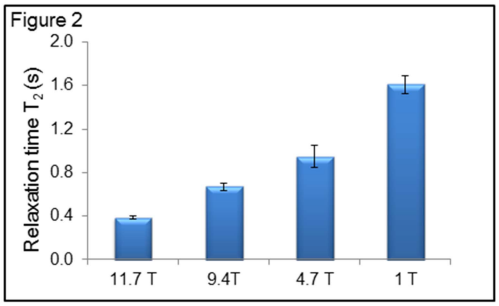
Sample name	n	Range of T_1 (s)	Range of T_2 (s)	Range of [Protein] (mg/dL)	Range of [Cu] (µM)	Range of [Fe] (µM)	Range of [Mn] (µM)	Range of [Zn] (µM)
Saline	3	4.1 – 4.5	2.9 – 3.4	0	0	0	0	0
Control patients	3	3.9 – 4.4	2.0 – 2.2	26 - 66	0.14-0.19	< 0.54	< 0.02	0.23 – 0.31
HAM/TSP patients	4	3.9 – 4.5	1.6 – 1.8	28 – 71	0.17 – 0.27	0.90 – 1.79	< 0.02	-
MS patients	8	3.7 – 4.0	1.2 – 2.0	18 – 92	0.14 – 0.32	< 0.54 – 1.07	< 0.02	0.21 – 1.38
Monkey	3	3.9 – 4.2	1.4 – 2.0	9 - 11	-	-	-	-

Figure 1



DISCUSSION In this study we were looking for the compound that is able to significantly change CSF T_2 relaxivity. Our results suggest that metals are too low concentrated to significantly change the CSF T_2. Compound such as lipids and specific proteins will be investigated. T_1 and T_2 *in vitro* measurements are in agreement with literature[7-8-9]. Hopkins and al., have shown a T_1= 4.3 s, and T_2= [1.8-2.2] s measured in humans *in vivo* at a very low field (0.15 and 0.6T)[7]. That is also in agreement with our T_2 *in vivo* measurement at low field (1T). However, our results suggest that *in vivo* T_2 value at high field is incorrect and that low field is more optimal to quantify CSF relaxivity *in vivo*. These data are important for the development of new MRI sequence for CSF segmentation and for possible detection of any molecular substrate of neurodegeneration within the CSF.

Figure 2



REFERENCES [1]Abdullah et al., Conf Proc IEEE Eng Med Biol Soc, 2013; [2]Gao et al., Neuroimage, 2014; [3]Hodel et al., Eur Radiol, 2013; [4]Poh et al., 2012; [4] ; [5]Prasloski et al., Magn Reson Med, 2012 [6]Bradford, Anal Biochem, 1976; [6]Hopkins et al., Magn Reson Med, 1986; [7]Larsson et al., Magn Reson Med, 1987 ; [8]Jezzard et al., Radiology, 1996.