Quantifying myelin kinetics in healthy subjects using deuterium labeling.

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INTRODUCTION

Demyelinating diseases, such as multiple sclerosis (MS), are characterized by an increased breakdown of myelin with a subsequent failure of the remyelination process. Enhancement of remyelination may improve recovery after an exacerbation¹. However, direct enhancement of remyelination can only be shown when myelin turnover rate can be quantified. The turnover rate of biomolecules can be determined by quantification of deuterium labeling after chronic administration of deuterated water (D₂O). Although the labeling of myelin cannot be determined directly in vivo, typical breakdown products or myelin precursors such as beta-galactosyceramide (BGaIC) can be measured in cerebrospinal fluid (CSF)².

METHODS

- 6 healthy volunteers
- Daily 120mL 70% D₂O, 70 days
- 5 lumbar punctures (days 35, 70, 93, 167 and 548 or 714)
- LC/MS/MS System for BGaIC analysis in CSF³
- BGaIC turnover rate estimated using non-linear mixed effects modeling

RESULTS

Although a high deuterium fraction of body water was observed (up to 3.9%, see figure 2), the deuterium fraction measured in BGaIC was markedly lower (up to 0.14%, see figure 3). The deuterium fraction in GaIC remained relatively stable during the study period, in subjects 1, 2, 4 and 5 even 100 days after the last dose of D₂O. A compartment turnover model best characterized the deuteration of body water and BGaIC. The differences in BGaIC deuteration were explained by interindividual variability in body water turnover. The estimated turnover rate of BGaIC is 413 days (352 - 499, 95% confidence interval).

CONCLUSIONS

A slow rate-limiting biochemical step is suggested by the data and estimation of BGaIC turnover rate. This is likely due to the production and/or degradation of myelin. The estimated BGaIC turnover rate is a potential, quantitative biomarker for myelin kinetics. Further research:
- Repeat study in MS patients, eventually with remyelinating compound
- This approach may be applicable for other CSF biomarkers.