Relationship between serum 24-hydroxycholesterol and brain water content, myelin water fraction, and T_1 relaxation in different stages of MS

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Abstract (2490/2500 characters with spaces, excluding headings)

Background:

Conventional MRI's limited sensitivity and specificity for MS pathology drives the development of more sophisticated imaging approaches to quantify damage in lesions, normal appearing white matter (NAWM) and diffusely abnormal white matter (DAWM). However, limited MRI resources in many places around the world, as well as a desire for additional objective metrics related to MS tissue damage, warrants the exploration of potential serum biomarkers that may reflect MRI abnormalities and support clinical management.

In blood, 24-hydroxycholesterol (24S-HC) is a known marker of neuronal metabolism and CNS cholesterol efflux. Increased 24S-HC may represent demyelination/neurodegeneration. Most 24S-HC crosses the blood brain barrier into the circulation before metabolism by the liver, thereby allowing a window into CNS oxysterol homeostasis.

Objectives: **To examine the relationship between serum 24S-HC and advanced MRI measures of brain water content (WC), myelin water fraction (MWF) and T_1 relaxation in different stages of MS.**

Methods:

103 MS participants (20 CIS, 33 RRMS, 30 SPMS, 20 PPMS) had 3T MRI and same-day blood sampling. Multiple linear regression by MS subtype assessed relationships between MRI measures in lesion, DAWM and NAWM and 24S-HC, while controlling for age, sex, EDSS, and disease duration (adjusted R^2 reported).

Results:

WC: Increased lesion WC was associated with increased 24S-HC in CIS (R^2=0.34, p=0.013).

MWF: Decreased MWF was associated with increased 24S-HC in RRMS (NAWM R^2=0.12, p=0.015; DAWM R^2=0.29, p=0.002; lesion R^2=0.27, p=0.003). Lesion MWF was also inversely associated with 24S-HC in CIS (R^2=0.24, p=0.042).

T_1: Decreased NAWM T_1 was weakly associated with increased 24S-HC in PPMS (R^2=0.18, p=0.045).

No significant relationships between 24S-HC and other MRI measures (normalized brain, lesion, thalamic, and deep GM volumes, cortical thickness) were observed.

Conclusions:

We found varying degrees of correlation between 24S-HC and lesion WC in CIS; MWF of NAWM, DAWM, and lesions in RRMS and CIS; and NAWM T_1 in PPMS. The strongest association between 24S-HC and lesion WC and MWF was seen in the earliest stages of MS (CIS, RRMS). This may support the relationship between

24S-HC and demyelination in MS. 24S-HC could potentially have utility as a supportive biomarker for assessing white matter pathology in different MS disease courses. Further research is needed to better understand and establish these relationships and define quantitative thresholds for clinical significance.