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Neuroimaging markers of Wilson disease

Wilson disease (WD) is a treatable metabolic disorder with systemic copper accumulation leading to disabling neurologic symptoms and distinct abnormalities on brain MRI. The most characteristic pathological changes in brain MRI include hyperintense lesions on T2-weighted images and atrophy. However, since the first brain MRI studies in WD, hypointense lesions in basal ganglia on T2/T2*-weighted images indicative of paramagnetic mineralization were also observed. The latter lesions may paradoxically become more apparent after anti-copper treatment initiation. It was hypothesized that T2-hypointensities may reflect either copper or iron cerebral deposits in WD.

To answer this question, we performed an MRI-histopathology correlation study analyzing brain slices from nine WD and six control cases. MRI protocol included high-resolution T2*-weighted imaging and quantitative measurement of R2* transverse relaxivity in the lentiform nucleus. Corresponding histopathological sections were examined using Turnbull iron staining combined with immunohistochemistry for macrophages or astrocytes. Additionally, copper and iron concentrations were measured and correlated with R2* values. We have shown that iron concentration in WD was increased compared to controls ($p<0.05$) and tightly correlated with T2* hypointensities in visual analysis as well as with R2* values ($R^2=0.80$, $p=0.001$). Conversely, copper concentration was not correlated with R2* values. The most pronounced iron deposits along with most severe pathological changes were observed in the putamen, where the iron concentration correlated with the elevated number of iron-containing macrophages suggesting that T2* hypointensities may reflect ongoing neuroinflammatory processes in WD. These findings contribute to a better understanding of the pathophysiology of WD and the interpretation of *in vivo* MRI findings.

Next, acknowledging the lack of validated neuroimaging markers in WD, we have developed a visual rating scale for semi-quantification of radiologic severity of WD. The proposed WD brain MRI severity scale consists of acute toxicity and chronic damage sub-scores from predefined brain structures. The former, calculated by summing scores of T2-hyperintensities, is partially reversible with treatment. The latter, representing the sum of scores of T2-hypointensities (i.e. iron deposits) and brain atrophy, reflects pathology that is not readily reversible. In this work, the reliability and construct validity of this scale was assessed using routine clinical MRI images from 39 WD patients. We have shown that inter-rater agreement was good and that the theoretical assumptions for using separate sub-scores for reversible and irreversible MRI abnormalities are correct. The Unified WD Rating Scale (UWDRS) score measuring clinical severity was associated only with chronic damage sub-score ($p=0.005$). The proposed neuroimaging scale, thus, reflects severity of brain damage and can be used as a surrogate marker of neurological severity.

In the last study, we have analyzed the contributions of regional cerebral atrophy and iron accumulation to neurological severity in WD. This study was also motivated by the need of validated quantitative imaging marker of disease severity. We have examined 29 WD patients on a long-term anti-copper treatment using brain MRI and UWDRS. The MRI protocol included high-resolution T1-weighted imaging to provide quantitative morphometric information and quantitative susceptibility mapping which is sensitive to iron deposits. Using complementary region-based and whole-brain analyses we provided a novel perspective on seeing atrophic changes in WD which involve large regions of white matter in addition to volume loss in the deep grey matter. We have identified putamen atrophy as a factor with tightest and most consistent association with neurological severity in WD ($R^2=0.35$, $p<0.001$). Conversely, iron deposits were not associated with clinical severity in any deep grey matter region. The chronic-damage MRI sub-score was also negatively associated with the UWDRS score ($R^2=0.26$, $p=0.003$) but the model including putamen volume was slightly superior (see Figure 1). Putamen volume can be used as a robust surrogate marker of clinical severity in future clinical trials in WD.

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Figure 1: Regression analysis of square root transformed UWDRS score and putaminal volume (left) and MRI score (right); linear regression fits are shown as blue lines, whereas the grey areas represent their 95% confidence bands. Abbreviations: UWDRS = Unified Wilson disease rating scale.