

Pathological correlates of cortical changes in Alzheimer's Disease at ultra-high field MRI

Bulk, M., Van der Graaf, L., Mulders, C., Natté, R., Hassan, W., Dijkstra, J., Van der Voorn, P., Van de Berg, W., Van Buchem, M., and Van der Weerd, L.

Leiden University Medical Center, Departments of Radiology & Human Genetics, Albinusdreef 2, 2300 RA Leiden, The Netherlands. L.van_der_Weerd@lumc.nl

Research question and background

The pathophysiology of Alzheimer's Disease (AD) is still not fully understood and non-invasive methods are important to increase our understanding of the disease and detect AD in vivo at an early stage. Previous studies showed an increased iron accumulation around amyloid plaques which induced a magnetic susceptibility effect, visible as hypointense foci in the cerebral cortex in human post-mortem brain slices on susceptibility-weighted (SW) magnetic resonance imaging (MRI). Moreover, the histological correlation showed that the pattern of the susceptibility-weighted contrasts in the temporal lobe of AD patients does not co-localize with amyloid plaques or neurofibrillary tangles, but with microglia- and myelin-associated iron accumulation and with an altered myelin cytoarchitecture. The observed correlation between SW MRI contrast changes, myelin changes and increased iron accumulation in AD cortices suggests a disturbed iron accumulation and myelin architecture in AD. Therefore, in this study post-mortem research on the correlation between ultra-high field MRI and AD pathology in different brain regions is done to further investigate the role of iron and myelin on SWI contrast and their changes in AD patients.

Methods and tissues used

To investigate the correlation between ultra-high field MRI and histology tissue samples of four different cortical regions (frontal, occipital, parietal and temporal) from early-onset and late-onset AD patients as well as age- and gender-matched controls were obtained from the Netherlands Brain Bank. From each subject of each cortical region a 7T SW image was acquired and 20 μm sections were used for histological stainings. The SW images were analyzed using a scoring method to define normal and abnormal cortices. To assess the histological correlates, the histological slides were registered to the MR images using an automatic registration pipeline. The myelin architecture was quantified using standardized stereometric techniques in collaboration with VUMC.

Results and conclusion

Preliminary results of SWI analysis of the frontal cortex showed that the diffuse hypointense bands were more frequently found in the frontal cortex of AD patients compared to controls. The histological correlation of the frontal cortex showed that the SW images correlated best with the iron and myelin distribution. For the other samples, we expect that the diffuse hypointense band is more frequently present in the SWI images of the temporal lobe of AD patients and will be spatially correlated with iron and myelin. Quantification of the myelin architecture with stereometric techniques showed a disturbed cytoarchitecture of gray matter myelin in the frontal lobe of AD patients. Both with SWI and stereometric techniques, striking differences were observed between early-onset and late-onset AD patients. From this study we may conclude that SWI may serve as a biomarker for AD. Secondly, SWI and the underlying pathological changes in iron and myelin cytoarchitecture have a distinctly different pattern for early- and late-onset AD, likely reflecting different pathogenic mechanisms.

control **late-onset AD** **early-onset AD**

MRI



iron



myelin

