Differentiating LATE from Alzheimer's Disease in the Era of Anti-Amyloid Monoclonal Antibody Treatment: A Novel Machine-Learning Approach

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Limbic-predominant Age-related TDP-43 Encephalopathy (LATE) is an emerging dementia phenotype that mimics Alzheimer’s Disease (AD)-type amnestic dementia syndrome. However, LATE neuropathological change (LATE-NC) and AD neuropathological change (AD-NC) have distinct clinical temporal trajectories; AD-NC is characterized by amyloid and tau pathology, while LATE-NC is characterized by TDP-43 proteinopathy with absence of amyloid and tau pathology. Hence, it is critical to differentiate these two similar clinical entities. Yet, while PET imaging to quantify amyloid and tau burden in the brain has been well developed, non-invasive probes for TDP-43 pathology are lacking. This study thus sought to identify MRI-based non-invasive imaging biomarkers to differentiate histopathologically-determined LATE-NC from AD-NC, focusing on four key aspects of the radiomic workflow; ROI segmentation, feature extraction, analysis, and classification. Using a case-control retrospective case series of 166 patients with histopathologically-proven LATE-NC or AD-NC in the National Alzheimer’s Coordinating Centre cohort, a random forest classifier was performed on 1130 radiomic features extracted from hippocampus segmentations of patients’ last available T1-weighted MRI scans obtained prior to their demise. The proposed model differentiates LATE-NC from AD-NC using ante-mortem medical images with 88% accuracy, 89% precision, 88% recall, 88% F1 score and 83% Area under ROC Curve. This novel machine-learning approach recognizes MRI-based non-invasive imaging biomarkers for early clinical differentiation of LATE-NC from AD-NC and has the potential to identify subgroups of patients diagnosed with clinical AD with LATE-NC, which are less likely to benefit from anti-amyloid monoclonal antibody therapy.

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