Appendix e-1

Supplemental methods

Study population

Clinical eligibility criteria for ADNI MCI cases were age 55-90, Hachinski ≤ 4, Mini-Mental State Examination (MMSE) 24-30, subjective memory concern, objective memory loss measured by adjusted delayed recall scores of one paragraph from Wechsler Memory Scale Logical Memory II, a Clinical Dementia Rating (CDR) score of 0.5, absence of significant levels of impairment in other cognitive domains, preserved activities of daily living, and absence of dementia. ADNI Cognitively Normal subjects were defined as age 55-90, MMSE scores between 24-30, a CDR of 0, and not meeting criteria for depression, MCI or dementia. Those with co-morbid medical, psychiatric or neurological conditions likely to significantly affect participation in the study were excluded. Those with evidence of infection, infarction (including multiple or strategic lacunes), or other focal lesions on baseline MRI were also excluded.

Baseline medical history, vascular risk factor, blood pressure and medication data

All data regarding participant baseline medical history, vascular risk factors, blood pressure and medications was downloaded from the ADNI website (www.adni.loni.usc.edu). ADNI participant's current and past medical history was documented at the initial ADNI visit by a study physician at each participating center based on a detailed patient interview including standardized medical history questionnaire, physical examination and review of available medical records. The database generated from this information was reviewed by a physician participating in the current study (B.-W.W.) and relevant details including history of vascular

disease, vascular risk factors, vascular prevention medication, and baseline blood pressure were recorded. Diagnosis and treatment of medical conditions including vascular risk factors was by a variety of non-study community and hospital-based treating physicians as part of usual clinical care and not a pre-defined aim of the ADNI study.

Derivation of periventricular white matter hyperintensities rating scale

In a preliminary analysis of 210 randomly selected ADNI MCI cases we rated white matter hyperintensity burden using previously reported white matter rating scales including the Schelten[1], Fazekas[2] and ARWMC[3]. The results are described in table e-1. We found no association between CSF-Aβ positivity (defined as <192pg/ml) with total Schelten score, total Fazekas score, total ARWMC score or total white matter hyperintensity burden estimated using a volumetric technique. The Schelten periventricular subscore (p=0.05), Fazekas periventricular subscore (p=0.12) and ARWMC parieto-occipital sub-score (p=0.12) and total white matter hyperintensity burden estimated using a volumetric technique (p=0.08) showed the strongest assocations with CSF-Aβ positivity but did not reach our predefined significance level of $p<0.05$. Scheltens, Fazekas and ARWMC visual rating scales have previously been shown to display ceiling effects and poor discrimination of absolute lesion volume compared to a semiautomated volumetric technique[4]. Although the correlation between periventricular white matter hyperintensities (PVWMH) and deep white matter hyperintensities has been shown to be strong[5], deep white matter lesion burden are more likely than PVWMH to have contributions from other pathologies such as embolic stroke and therefore may be less sensitive in detecting associations with neurodegenerative disease[5]. Quantifying white matter lesion burden by semi-automatic volumetric analysis can be time intensive, for example, requiring de-selection of erroneously

included regions such as areas of lacunar or large artery infarction and adjustments to adequately include areas with lower level hyperintensity, as is frequently encountered in the occipital region. In addition methods that only estimate total cerebral burden of white matter hyperintensities may not detect regional associations with neurodegenerative pathology. To overcome these potential limitations we sought to develop a visual rating scale that could be rapidly and reproducibly applied to rate PVWMH burden in frontal, parietal and occipital areas. To reduce ceiling effects in the frontal and parietal scoring we used a scalar measurement without a maximal cut-off. In the frontal and parietal areas the ventricular wall runs close to perpendicular on several axial cerebral MRI slices facilitating use of a scalar cross-sectional measurement of PVWMH (see figure 1). In the occipital area there is variable orientation of the ventricular wall with respect to axial MRI slices due to the geometry of the occipital horn of the lateral ventricle. We therefore found a semi-quantitative visual scale (see figure 2) to be more reliable than a single measurement as was used for frontal and parietal PVWMH. We chose a 7-point scale for occipital PVWMH to reduce ceiling effects.

MRI image analysis for periventricular hyperintensities

To increase inter-rater reproducibility the measurement line for frontal and parietal PVWMH was drawn parallel to the ipsilateral corpus callosum genu or splenium for frontal and parietal lesions respectively. Measurements taken from slices on axial imaging which transect PVWMH along planes parallel or tangential to the ventricular wall may over-estimate burden of disease. We therefore took measurements from the slice and side with greatest burden of disease lying between 5-20mm below the most superior border of the ventricles i.e. where axial slices typically transect PVWMH perpendicular to the frontal and parietal ventricular walls. Slices that appeared

to transect PVWMH longitudinally were not used for measurements. WMH surrounding lacunar infarcts were also not used for the purpose of rating PVWMH. The intensity of PVWMH can be variable and deciding where the furthest extension of PVWMH towards the cortical surface is can lead to inter-rater variability. After trialing a variety of rules for measuring the furthest extent of PVWMH we found the most reliable definition used the area of obvious WMH visible furthest from the ventricular tip which is still bounded within the cap-like distribution typical of PVWMH (see figure e-1). Discrete white matter hyperintensities which were separated from the ventricle by areas of normal appearing white matter were not used for measuring PVWMH. Specifically it was necessary for all of the white matter along the measurement line to appear hyperintense compared to regions of normal appearing white matter in other locations but the degree of hyperintensity could be heterogeneous. Using this method may better take account of the variable severities of periventricular white matter injury in the same patient. Including only PVWMH with entirely homogenous signal intensity does not account for the underlying heterogeneous pathophysiology of WMH progression[7-9]. Occipital PVWMH are often of lower signal intensity than that usually found in the parietal and frontal areas and appropriate windowing of images may be necessary to accurately visualize the extent of lesions in this area (see figure 2).

Supplemental references

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