Use of CSF amyloid for detecting cortical amyloid deposition: a multicenter study

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Background: There is a large inter-laboratory variance in local CSF beta amyloid (A β)1-42 cut-points used for clinical and research purposes. Variability may be caused by variability in pre-analytical procedures in measuring CSF markers or approaches to calculate cut-points. We aimed to define an optimal CSF A β 1-42 cut-point for detection of cortical amyloid deposition. Furthermore, we compared concordant and discordant cases. **Methods:** We included 434 subjects (57 controls, 99 MCI patients, 196 Alzheimer's disease (AD) patients and 82 other dementia patients) with available CSF and PIB-PET data from 5 centers. We used local cut-points and calculated optimal cut-points for each center that best predicted cortical amyloid burden using the Youden index. Cortical amyloid burden was detected by local visual rating of PIB-PET scans. An inter-site rater study of 20 PIB-PET scans showed a 100% accuracy. **Results:** Local cut-points for CSF Aβ 1-42 levels varied between 400-550 pg/ml. Their sensitivity for detection of cortical amyloid deposition ranged between 0.47-0.80 and specificity between 0.68-0.91. Calculated optimal cut-points that maximised the Youden index varied between 521-616 pg/ml, with a sensitivity ranged between 0.84-0.95 and specificity between 0.58-0.91. The optimal cut-point in the pooled sample was 557 pg/ml with a sensitivity and specificity of 0.87 and 0.79, respectively. Using the optimal CSF Aβ 1-42 cut-point, concordance between amyloid biomarkers was 86%. Of the 35 discordant subjects with normal CSF A β 1-42 and positive PIB-PET, 50% showed borderline CSF A β 1-42 levels. Furthermore, 62% showed an abnormal CSF tau, 48% was APOEε4 carrier, and >90% was diagnosed with MCI or AD. Of the 33 discordant subjects with abnormal CSF A β 1-42 and negative PIB-PET, 16% showed an abnormal CSF tau, 64% was APOEε4 carrier and 49% was diagnosed as non-AD dementia. **Conclusions:** Compared to clinical-based cut-points, the use of cortical amyloid deposition to define CSF A β 1-42 cut-points overall decreased inter-site variability and increased sensitivity and specificity. This suggests that the way clinical cut-points have been calculated introduces substantial variability. Analysis of discordant cases suggests that subjects with abnormal CSF A β 1-42 but negative PIB-PET may be less likely to have AD-related amyloid pathology than subjects with normal CSF A β 1-42 but positive PIB-PET.