Quantification Supports Amyloid PET Visual Assessment of Challenging Cases: Results from the AMYPAD Diagnostic and Patient Management Study

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Abstract: Several studies have demonstrated strong agreement between routine clinical visual assessment and quantification, suggesting that quantification approaches could support assessment by less experienced readers or in challenging cases. However, all studies to date have implemented a retrospective case collection, and challenging cases were generally underrepresented.

Methods: We included all participants (n = 741) from the AMYPAD diagnostic and patient management study with available baseline amyloid PET quantification. Quantification was done with the PET-only AmyPype pipeline, providing global Centiloid and regional z scores. Visual assessment was performed by local readers for the entire cohort. From the total cohort, we selected a subsample of 85 cases for which the amyloid status based on the local reader's visual assessment and the Centiloid classification (cutoff = 21) was discordant or that were assessed with low confidence (i.e., ≤3 on a 5-point scale) by the local reader. In addition, concordant negative (n = 8) and positive (n = 8) scans across tracers were selected. In this sample (n = 101 cases; [18F]flutemetamol, n = 48; [18F]florbetaben, n = 53), the visual assessments and corresponding confidence by 5 certified independent central readers were captured before and after disclosure of the quantification results.

Results: For the whole AMYPAD diagnostic and patient management study cohort, overall assessment by local readers highly agreed with Centiloid status (κ = 0.85, 92.3% agreement). This was consistently observed within disease stages (subjective cognitive decline–plus, κ = 0.82, 92.3% agreement; mild cognitive impairment, κ = 0.80, 89.8% agreement; dementia, κ = 0.87, 94.6% agreement). Across all central reader assessments in the challenging subsample, quantification of global Centiloid and regional z scores was considered supportive of visual reads in 70.3% and 49.3% of assessments, respectively. After disclosure of the quantitative results, we observed improvement in concordance across the 5 readers (baseline κ = 0.65, 65.3% agreement; κ after disclosure = 0.74, 73.3% agreement) and a significant increase in reader confidence (baseline mean (M) = 4.0 vs. M after disclosure = 4.34, Wilcoxon statistic (W) = 101,056, P < 0.001).

Conclusion: In this clinical study enriched for challenging amyloid PET cases, we demonstrate the value of quantification to support visual assessment. After disclosure, both interreader agreement and confidence showed significant improvement. These results are important considering the arrival of antiamyloid therapies, which used the Centiloid metric for trial inclusion and target engagement. Moreover, quantification could support determination of amyloid-β status with high certainty, an important factor for treatment initiation.

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