AMYPAD Deliverable 3.14
Phase II/III validation of amyloid PET on clinical repositories

Publishable Summary

Alongside AMYPAD's ambitious aims of data collection is the necessary validation of amyloid positron emission tomography (PET) on clinical repositories. This document outlines the motivation, process and results of this task for the benefits of both AMYPAD as a Consortium and the general research community. The broad aims of this work are threefold:

1) Investigate the effect of brain atrophy on amyloid positivity in controls and cognitively impaired
2) Investigate the association between topography of amyloidosis and overall positivity
3) Define quantitative criteria for amyloid positivity (global and regional) to be used in the prospective phase of the diagnostic value study as a possible secondary measure

Aim 1 is addressed through further examination of the [18F]Flutemetamol/Florbetaben Phase III and autopsy studies. The performance of both tracers was evaluated against pathology as standard of truth (SoT) using blinded PET scan interpretations by independent trained readers. The SoT measures included analysis of the post-mortem tissue for the presence of neuritic and diffuse beta-amyloid plaques using a combination of modified Bielschowsky silver staining and immunohistochemistry. The overall conclusion for both tracers were that the majority of cases were either true negative or true positive when compared to amyloid pathology as the SoT. False negatives were broadly due to confounding atrophy and false positives due to diffuse amyloid. In summary, confounding atrophy can have a small negative effect on overall sensitivity for amyloid status.

Aim 2 has been addressed through recent publications on behalf of the AMYPAD consortium: Collij et al (2020) and Fantoni et al (2020). In the first study, a staging model successfully classified the level of amyloid burden in >3,000 individuals across cohorts and radiotracers. Furthermore, it detected pre-global amyloid burden and distinct risk profiles of cognitive decline within globally amyloid-positive individuals. The second study was a state-of-the-art review covering post-mortem pathology work, studies comparing amyloid PET signal with histology-based regional Thal staging, ranking of regional amyloid signal by PET-only studies and finally studies based on longitudinal PET Imaging. Summary outcomes were (i) The regional-temporal evolution of amyloid pathology may enable the earlier identification of subjects in the AD pathologic continuum; (ii) Cortical deposition generally precedes striatal pathology, and in PET only studies, medial cortical regions are seen to accumulate amyloid earlier than lateral regions; and (iii) Models for staging amyloid pathology could improve subject selection into secondary prevention trials and support visual assessment in clinical routine.

Aim 3 is covered in the plans for future AMYPAD image analysis where we take direction from the retrospective assessments in Aim 1 and have made the following plans:

• Understanding discordance between visual assessment and quantification. In collaboration with our Karolinska partner site, the AMYPAD consortium is investigating possible factors that explain discordance between visual assessment by local readers and Centiloid (CL) quantification, both a global and regional level. The effect of atrophy in this discordance is a key aspect of interest.

• Visual read of local reads versus expert reads. This project aims to investigate the value of quantification to support the assessment of difficult amyloid PET scans, either based on low confidence of the local reader or based on discordance between visual assessment and CL quantification. Reason for low confidence has been recorded and will be described per diagnostic group. For this project, DPMS scans will be assessed by 5 expert readers to record a central read. In addition, the readers are provided with regional z-scored data based on the AMYPIPE pipeline and global CL value and asked whether quantification supported their final assessment and/or improved their confidence.

• Case analysis of images in our DPMS subject to atrophy and assess whether automated quantification creates an over or under segmentation. As a body of work, these studies have highlighted the clinical usefulness of amyloid PET. Hopefully, this work and the associated future plans will improve the quality of health care through widespread clinical implementation and increased reimbursement for these tests by health insurance providers.

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