IC-P-013 DIAGNOSTIC VALUE OF AMYLOID IMAGING IN EARLY ONSET DEMENTIA

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Background: In early onset dementia approximately one out of three patients has an atypical clinical presentation, which substantially complicates correct etiological diagnosis. [18 F]Flutemetamol PET, an investigational imaging agent, is being studied for detection of amyloid deposition, a pathological hallmark of Alzheimer's Disease (AD). In our ongoing study we examine the diagnostic value of [18 F]Flutemetamol PET in assessing patients with early onset dementia. **Methods:** We included 80 patients with early onset dementia (age <70 years) and physician diagnostic confidence less than 90% after a full routine diagnostic work-up for dementia. All patients underwent a [18 F]Flutemetamol PET scan which were visually assessed as amyloid positive or negative. Scans were performed between 90 and 110 minutes after injection of approximately 185 MBq [18 F]Flutemetamol. Before and after disclosing PET results to the patient's managing physician, clinical diagnosis and confidence in this diagnosis was determined. Also, the impact on patient healthcare management was assessed. **Results:** [18 F]Flutemetamol scans were positive in 48 out of 63 (76%) patients diagnosed (pre-PET imaging) with AD and 4 out of 17 (24%) patients diagnosed with other dementias. Overall, confidence in etiological diagnosis increased from 76±12% to 90±16% after disclosing PET results ($p<0.001$). Access to PET results led to a change in diagnosis in 16 (20%) patients. In 11 out of 13 patients, a negative PET scan caused a change of the initial AD diagnosis to another dementia. In 3 out of 4 other dementia patients, the initial diagnosis was changed to AD after receiving a positive PET scan. In 27 (34%) patients, PET results led to a change in patient healthcare management (i.e., 25 patients had their medication changed and 9 patients received additional care). These patients predominantly had a clinical diagnosis of AD. For 13 patients additional ancillary investigations were planned after access to the PET scan results. **Conclusions:** [18 F]Flutemetamol PET resulted in changes in the diagnostic process work-up of early onset dementia patients and the diagnostic confidence of the managing physicians. Especially in patients diagnosed with AD prior to PET, a negative PET scan resulted in more changes in clinical diagnosis and patient management.

IC-P-014 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 Mild Cognitive Impairment 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 Aβ1-42 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 Aβ1-42 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.

IC-P-015 NEW TOOLS FOR AMYLOID PLAQUES DETECTION BY MRI: GADOLINIUM-VHH ANTIBODY CONJUGATES

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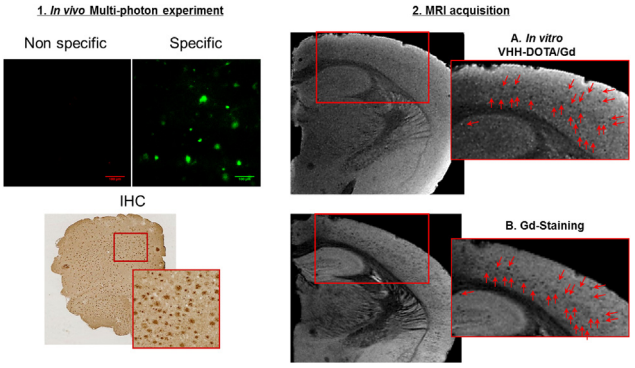
Background: The early diagnosis of Alzheimer's disease (AD) is critical for the evaluation of new therapies and for patient follow-up. Aggregation of Aβ 1-40, Aβ 1-42 peptides in amyloid plaques, one of the major hallmarks of the pathology, begins more than 15years before neuropsychological symptoms. Few methods have been developed to detect amyloid plaques by MRI but they always required an invasive process to open the blood brain barrier (BBB). Heavy chain only antibody fragments (VHH), because of their small size and their basic isoelectric point, have the potential to cross the BBB. Hence, in order to detect amyloid plaques by MRI, we developed VHHs with high specificity against Aβ 1-40, Aβ 1-42. First, we evaluated the BBB crossing by in vivo multi-photon imaging after conjugation of our VHHs to a fluorochrome. Then, gadolinium (Gd) was conjugated to VHHs via a DOTA cage and the resulting contrast agent (VHH-DOTA/Gd) was evaluated by MRI. **Methods:** Conjugates were synthesized by conjugation of Alexa-Fluor488 or a DOTA/Gd synthon on VHHs. Conjugates were monitored by HPLC/MS, and binding properties were confirmed by ELISA and IHC. PS2APP mice aged of 90-100weeks were used (n=2/experiment). In vivo multi-photon experiments were realized after intravenous injections of VHH-AlexaFluor488. MRI acquisition were recorded following two different protocols 1) in vitro incubation of one hemisphere with VHH-DOTA/Gd (0.1mg/ml equivalent to 0.1mM of Gd) overnight, 2) Gd-staining, a reference technique to reveal amyloid plaques by soaking the hemisphere in a Gd-solution (2.5mM - 48h). **Results:** Live multi-photon imaging following intravenous injection showed gradual extravasation of the fluorescent VHHs from blood vessels and penetration in brain parenchyma with an exquisite tropism for amyloid plaques, as confirmed by IHC (Figure 1). MR images obtained after in vitro

incubation with VHH-DOTA/Gd showed numerous hypointense spots in the cortex (Figure 2A). Moreover, several hypointense spots were colocalised (red arrows) with amyloid plaques revealed by the reference technique of Gd-staining (Figure 2B). **Conclusions:** This study demonstrates that VHHs cross the BBB, label amyloid plaques in vivo and can be detected by MRI following conjugation with a contrast agent. VHHs thus appear as promising tools with translational value for in vivo detection of amyloid deposits.



IC-P-016 AMYLOID PLAQUES DETECTION BY MRI: COMPARISON OF FIVE MOUSE MODELS OF AMYLOIDOSIS

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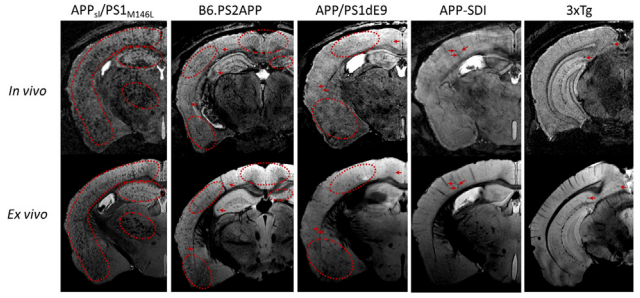
Background: Alzheimer's disease (AD) is characterized by two complementary brain lesions: amyloid plaques and neurofibrillary tangles. Amyloid plaques occur up to 20years before the first clinical signs of the disease and their detection is thus critical for an early diagnostic and to follow-up potential treatments. We developed methods of ex-vivo or in-vivo amyloid plaques detection based on the use of a non-targeted gadolinium (Gd) contrast agent for magnetic resonance imaging (MRI). Even if numerous mouse models of amyloidosis have been developed, the age of appearance, the size and the composition of the plaques in these models are different. Here, we compared the MRI detection of amyloid plaques by in-vivo and ex-vivo Gd-staining in different strains of mouse model of amyloidosis. **Methods:** Five strains of mice developing amyloid plaques before 10months were used: APP sl/PS1 M146L, APP/PS1dE9, B6.PS2APP, APP-SDI and 3xTg (APP swe/PS1 M146VKI/Tau P301L) aged of 14-15months (n=2/strain). Mice received an intracerebroventricular (ICV) injection of Gd (500mM, 1µl/side) and were imaged by in-vivo MRI one hour later. They were then sacrificed and their brains were extracted and incubated in a Gd solution (2.5mM - 48h) before ex-vivo high-resolution MRI. **Results:** Following in-vivo ICV infusion of Gd, MR images show numerous hypointense spots (upper pictures) which were previously demonstrated to be amyloid plaques (see Petiet et al., 2012 for examples). The number, size and contrast of the hypointense spots were highly variable in the different strains. This inter-strain difference was confirmed by the high signal/noise ratio ex-vivo Gd-stained MR images (lower figures). Plaques were more visible in APP sl/PS1 M146L > B6.PS2APP > APP/PS1dE9 > APP-SDI > 3xTg mice and only few plaques appeared in the two latter strains. **Conclusions:** These results demonstrate that depending on the strain, amyloid plaques display highly different aspects in MRI. These differences appear to be mainly due to the size of amyloid plaques. The contrast/noise ratio of the plaques on MR images is also critical for the detection of the plaques. This parameter can be modulated by the composition of the plaques, for example by their iron concentration or the Aβ40/42 ratio that can modulate their hydrophobicity and interaction with the contrast agent.



IC-P-017 BLINDED VISUAL EVALUATION AND QUANTITATIVE SUVR THRESHOLD CLASSIFICATION OF [18F]FLUTEMETAMOL PET IMAGES IN JAPANESE SUBJECTS

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Background: Amyloid imaging data are often quantified using a method where target region to cerebellar cortex tracer uptake ratios (SUVRcer) are computed. We investigated the agreement between blinded visual evaluations (BIE) and quantitative analysis of [18 F]f lutemetamol in a Japanese population. **Methods:** Healthy volunteers (HV; n=25, 15 elderly healthy volunteer ≥ 55 years (EHV), 10 young healthy volunteers <55 (YHV)) and patients with probable Alzheimer's Disease (pAD; n=20) and amnestic mild cognitive impairment (aMCI; n=20) each underwent a 30min dynamic PET scan, starting 90min post injection of 185MBq [18 F]flutemetamol. A 3D T 1 MRI was also obtained. Image data was processed to allow for application of a template set of regions of interest to a 30 min summation image to estimate a global cortical average SUVRcer. The optimal threshold was estimated as the midpoint between the mean of pAD and EHV cohorts in terms of standard deviation for the global SUVRcer. BIE were performed by 5 Japanese and 5 non-Japanese independent board-certified readers to obtain the majority outcomes of the ten readers. T he diagnostic capability of BIE and of global SUVRcer for differentiating AD from HV was evaluated, together with agreement between BIE and global SUVRcer. **Results:** Optimal threshold for discriminating pAD from HV was 1.391 for the global cortical SUVRcer average. Sensitivity and specificity of discriminating pAD from HV in this cohort for BIE (majority outcome) were 90% and 100%, respectively, and for SUVR cer 90% and 100%. In the efficacy evaluation, the quantitative classification categorized 18 subjects as positive (18 pAD, 0 HV), all of these were classified as positive by BIE. 27 subjects were categorized as negative quantitatively (25 HV, 2 pAD) and also by BIE, resulting in a 100% agreement between BIE and quantification using this threshold. BIE categorized 10 of 20 aMCI subjects as positive, quantitative classification added three subjects to this category. **Conclusions:** Agreement between the visual and quantitative assessment of [18 F]flutemetamol images is high. While quantitative classification should not replace visual assessment, it may be useful as a tool for detecting early stages of amyloid accumulation.