

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

Marissa Deborah Zwan¹, Femke H. Bouwman², Wiesje M. Van der Flier³, Adriaan Lammertsma¹, Bart van Berckel¹, Philip Scheltens⁴, ¹VU University Medical Center, Amsterdam, Netherlands; ²Alzheimer Centre VU Medical Centre, Amsterdam, Netherlands; ³VU University Medical Center, Amsterdam, Netherlands; ⁴VU University Medical Center, Amsterdam, Netherlands. Contact e-mail: m.zwan@vumc.nl

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

Marissa Deborah Zwan¹, Juha Rinne², Steen Hasselbalch³, Alberto Lleó⁴, Bart van Berckel¹, Pieter Jelle Visser⁵, ¹VU University Medical Center, Amsterdam, Netherlands; ²Turku PET Centre, Turku, Finland; ³Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark; ⁴CIBERNED, IIB-Sant Pau, Barcelona, Spain; ⁵VUMC, Maastricht, Netherlands. Contact e-mail: m.zwan@vumc.nl

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 A β 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 A β 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 APOE ϵ 4 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 APOE ϵ 4 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

Matthias Vandesquille¹, Tengfei Li², Fani Koukouli², Christelle Ganneau², Uwe Maskos², Christian Czech³, Fiona Grueninger⁴, Charles Duyckaerts⁵, Benoît Delatour⁶, Sylvie Bay², Pierre LaFaye², Marc Dhenain¹, ¹CEA, Fontenay-aux-Roses, France; ²Institut Pasteur, Paris, AZIe-de-France, France; ³CNS Research, Hoffmann-La Roche AG, Basel, Switzerland; ⁴Roche, Basel, Switzerland; ⁵CRICM/ICM - Team "Alzheimer's and Prion Diseases" UPMC/Inserm UMR-S 975 - CNRS UMR 7225, Paris, France; ⁶CNRS, Paris, France. Contact e-mail: matthias.vandesquille@cea.fr

Background: The early diagnosis of Alzheimer's disease (AD) is critical for the evaluation of new therapies and for patient follow-up. Aggregation of A β 1-40, A β 1-42 peptides in amyloid plaques, one of the major hallmarks of the pathology, begins more than 15 years 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 A β 1-40, A β 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 90-100 weeks 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