Early detection of amyloid load using 18F-Florbetaben PET

Santiago Bullich1,2, Núria Roé-Velvé1,2, Marta Marquéu3,4,5, Victor L. Villemagne6, Ángela Sanabria1,4,5, Juan Pablo Tartari1,5, Oscar Sotolongo1,5, Vincent Dore6, Norman Koglin7, Andre Müller1,7, Andrew Perriton1,7, Susan De Santi1, Luis Tárraga2,3,4,5, Andrew W. Stephens1, Christopher C. Rowe1, John P. Seibyl8, Mercè Boada1,3,4,5

1 Life Molecular Imaging GmbH, Berlin, Germany; 2 On behalf of the AmyPAD consortium; 3 Fundació ACE Institut Català de Neurociències Aplicades, Alzheimer Treatment and Research Center – Universitat Internacional de Catalunya, Barcelona, Spain; 3 Centro de Investigación Biomédica en Red de Enfermedades Neurodegenerativas (CIBERNED), Instituto de Salud Carlos III, Madrid, Spain; On behalf of the FACiBHi study group; 5 Depts of Medicine and Molecular Imaging, Austin Health, Melbourne, VIC, Australia; 7 Life Molecular Imaging Inc, Boston, USA; 8 Enviros, New Haven, Connecticut, USA

Introduction

• Accurate measurement of Aβ deposition is critical in longitudinal interventional therapeutic trials of Aβ-modifying treatments for Alzheimer disease (AD).
• The amount of brain Aβ load is widely assessed in PET imaging by means of the SUV ratio (SUVR) because of its simplicity.
• Pathology-proven 18F-Florbetaben (FBB) SUVR abnormality cutoffs have been developed to discriminate between AD patients with established Aβ pathology and elderly Aβ-negative non-demented controls (SUVR 혹은 1.48 (Sabri et al. 2015)).
• However, observational research studies and interventional therapeutic trials focus on the early stages of Aβ deposition. A lower Aβ amount and extent may limit the use of previously developed SUVR cutoffs.

Objective

To develop and validate an FBB SUVR cutoff:
• to detect early Aβ deposition
• to identify those subjects that will likely accumulate Aβ over time
• to be used in the screening of clinical trials with asymptomatic population

Material and methods

Subjects

The samples of participants in this study included:
1) Young healthy controls (YHC). A sample of YHC subjects (n=154, 27.6±5.1 years (mean±SD)), which underwent an FBB PET scan were used to generate a SUVR cutoff for the detection of early Aβ deposition (SUVR 혹은 1.48). The cutoff was derived as two standard deviations above the mean SUVR in this sample of YHC. The previously reported cutoff for established Aβ pathology (SUVR 혹은 1.48, Sabri et al. 2015) and the SUVR 혹은 1.48, allowing defining three regions in the SUVR continuum: Aβ-negative subjects (<SUVR 혹은 1.48), early Aβ accumulation (“gray zone”) (SUVR 혹은 <SUVR 혹은<SUVR 혹은 1.48), and established Aβ deposition (SUVR >SUVR 혹은 1.48).
2) Subjective cognitive decline (SCD) subjects. A sample of subjects with SCD (n=166, 64.9±7.2 years (mean±SD)) from the FACEHi study (Aplicades et al. 2017) that underwent two FBB PET scans at baseline and at 2 years were included in this study to validate the SUVR cutoff generated.

Results

SUVR cutoff generation in YHC

The mean ± SD of the composite SUVR derived from the YHC sample was 1.16±0.04 (MRI-based ROIs). The resulting cutoff was SUVR 혹은 1.25 (Fig 1, Table 1).

With the standard CL ROIs the mean ± SD was 1.02±0.4, and the resulting cutoff was SUVR 혹은 1.09, CL 혹은 12 (Table 1).

Three regions in the SUVR continuum were defined as: Aβ-negative subjects (SUVR 혹은<1.25), early Aβ accumulation (“gray zone”) (1.25-1.48) and established Aβ deposition (SUVR >1.48) (Fig 1).

Cut-off validation in MCI subjects

The accumulation rates in the “gray zone” (0.94±1.6 %/year) and for “established Aβ deposition” (1.21 %/year) were significantly different from zero (Fig 4).

SUVR cutoff validation in SCD subjects

• SUVR histograms in a sample of SCD subjects showed a peak coincident with the gaussian function fitted to the sample of YHC (Fig 2).
• The histogram showed a tail with higher SUVRs that increased numbers at follow-up (Fig 2).
• The SCD subjects with SUVRs in the “gray zone” and established Aβ deposition had rates of Aβ accumulation statistically different from zero (p<0.001) (1.6±1.5 %/year and 2.3±2.4 %/year, respectively) (Fig 3).
• No accumulation statically different from zero was found in Aβ-negative subjects (0.2±1.5 %/year, p=0.08).

Conclusions

An SUVR range from 1.25 to 1.48 is optimal to detect early Aβ deposition and to identify subjects that are likely accumulating Aβ.

Only those subjects in the upper limit of the gray zone converted to AD after 4 -years. None of the Aβ-negative subjects converted to AD after 4-years clinical follow-up (Fig 4).

Fig 1. Histogram of the CSUVRs obtained from the YHC sample. A gaussian curve was fitted to this histogram. The cutoff was set at 2 SD above the mean SUVR. The previously validated SUVR threshold for established Aβ deposition is also represented.

Fig 2. CSUVR histograms of the SCD participants at baseline (left) and follow-up (right). The gaussian from the YHC sample has been plotted over each histogram (in red), as well as the gray zone (in blue) early detection threshold.

Fig 4. Histogram of the CSUVR for a sample of MCI subjects. The gaussian function derived from the YHC sample has been plotted over each histogram (in red), as well as the gray zone (in blue). Rate of Aβ accumulation in MCI subjects (and 95% confidence interval) in three regions in the SUVR continuum: Aβ-negative, gray zone and with established Aβ deposition (right panel).