18F-Flutemetamol PET post-stroke - a seven year follow-up study

Guri Hagberg (guhagb@vestreviken.no)
Vestre Viken HF https://orcid.org/0000-0003-2822-7701
Hege Ihle-Hansen
Oslo universitetssykehus Ulleval
Brynjar Fure
Centralsjukhuset Karlstad
Bente Thommessen
Akershus Universitetssykehus Nevroklinikken
Håkon Ihle-Hansen
Baerum sykehus
Anne Rita Øksengård
Baerum sykehus
Mona K. Beyer
Oslo universitetssykehus Rikshospitalet
Wyller MD
Oslo universitetssykehus Ulleval
Ebba Gløersen Müller
Oslo universitetssykehus Ulleval
Sarah T. Pendlebury
University of Oxford Nuffield Department of Clinical Neurosciences
Per Selnes
Akershus Universitetssykehus Nevroklinikken

Research article

Keywords: Stroke, cognitive impairment, cerebrospinal fluid, positron emission tomography, prognosis

Posted Date: December 26th, 2019

DOI: https://doi.org/10.21203/rs.2.19511/v1

Version of Record: A version of this preprint was published at BMC Neurology on May 8th, 2020. See the published version at https://doi.org/10.1186/s12883-020-01753-w.

Abstract

Background: Cognitive impairment (CI) with mixed vascular and neurodegenerative pathologies after stroke is common. The role of amyloid pathology in post-stroke CI is unclear. We hypothesize that amyloid deposition, measured with Flutemetamol (^{18}F-Flut) positron emission tomography (PET), is common in 7-year stroke survivors diagnosed with CI and, further, that quantitatively assessed ^{18}F-Flut-PET uptake after seven years correlates with amyloid-β peptide (Aβ□□) levels in cerebrospinal fluid (CSF) at one year, and with measures of neurodegeneration and cognition at seven years post-stroke.

Methods: 208 patients with first-ever stroke or TIA without pre-existing CI were included during 2007 and 2008. At one- and seven-years post-stroke, cognitive status was assessed, and categorized into dementia, mild cognitive impairment or none. Etiologic sub-classification was based on magnetic resonance imaging (MRI) findings, CSF biomarkers and clinical cognitive profile. At seven years, patients were offered ^{18}F-Flut-PET, and amyloid-positivity was assessed visually and semi-quantitatively. The associations between ^{18}F-Flut-PET standardized uptake value ratios (SUVr) and measures of neurodegeneration (medial temporal lobe atrophy (MTLA), global cortical atrophy (GCA)) and cognition (Mini-Mental State Exam (MMSE), Trail-making test A (TMT-A)) and CSF Aβ□□ levels were assessed using linear regression.

Results: In all, 111 patients completed 7-year follow-up, and 26 patients agreed to PET imaging, of whom 13 had CSF biomarkers from one year. Thirteen out of 26 patients were diagnosed with CI seven years post-stroke, but only one had visually assessed amyloid positivity. CSF Aβ□□ levels at one year, MTA grade, GCA scale, MMSE score or TMT-A at seven years did not correlate with ^{18}F-Flut-PET SUVr in this cohort.

Conclusions: Amyloid binding were not common in 7-year stroke survivors diagnosed with CI. Quantitatively assessed amyloid did not correlate with other measures related to neurodegeneration and cognition. Therefore amyloid pathology may not be a key mediator of neurodegeneration seven years post-stroke.

Background

Post-stroke cognitive impairment (CI) is caused by both vascular and neurodegenerative changes (1). Due to an aging population and a decline in post-stroke mortality, strategies for timely diagnosis and disease prevention are urgently needed (2–5). Post-stroke cognitive impairment follows different trajectories, and risk scores based on clinical and neuroimaging variables are promising (6, 7), but do not include amyloid biomarkers. Amyloid positivity has been associated with more severe cognitive decline post-stroke in small studies (8, 9), and might be included in future prediction models and individualized management.

Known risk factors for dementia in the normal population include neuroimaging variables such as β-amyloid deposition, medial temporal lobe atrophy (MTLA) and small vessel disease. The risk factors are additive, and there are several indications of mechanistic interactions (10, 11). Recent studies support the use of amyloid positron emission tomography (PET) in patients with uncertain diagnosis in a memory clinic setting (12–14), but studies are missing in the post-stroke population.

Amyloid biomarkers include cerebrospinal fluid (CSF) Amyloid-β peptide (Aβ□□) levels, and amyloid-binding PET tracers. CSF Aβ□□ levels are established biomarkers of Alzheimer´s disease, and constitute the central biomarker

for amyloid plaque formation (15). ^{18}F-Flutemetamol (^{18}F-Flut) is increasingly used in dementia diagnostics, as it exhibits high affinity binding for fibrillary amyloid (16, 17). A negative ^{18}F-Flut-PET examination indicates sparse or no fibrillar beta amyloid, which may be incompatible with a neuropathological diagnosis of AD (18). ^{18}F-Flut-PET and CSF Aβ□□ levels have shown to be highly correlated (14, 19–21). In animal models, there has been a synergistic relationship between inflammation induced by stroke-related ischemia and beta-amyloid deposits (22–24), but this association has not been studied in humans (25, 26). As amyloid deposition increases with age (11), and theoretically might accelerate due to inflammation related to stroke, a quantitatively assessed amyloid PET might be more useful than binary visually assessments, by allowing a continuous measurement in different brain regions. MTLA and cortical atrophy are well described in both AD and pure cerebrovascular disease (27–29), but there is still no consensus regarding the contribution of amyloid pathology to post-stroke neurodegeneration and cognitive impairments (30–32). A recent study from Pendlebury et al shows that Apolipoprotein E4 e4/e4 genotype is associated with increased risk of dementia after stroke suggesting a role for neurodegeneration (33). The Atherosclerosis Risk in Communities (ARIC)-Pet Amyloid Imaging Study showed that an increasing number of midlife vascular risk factors were associated with amyloid deposition, consistent with a role of vascular disease in the development of AD (34).

The reported prevalence of visually assessed amyloid positivity rage from 5% in 2/38 MCI patients assessed 6 months post-stroke (35), to 40% in 4/10 post-stoke dementia patients (36). Of the seven studies identified (8, 9, 31, 32, 36, 37), only one used ^{18}F-Flut-PET (35).

In the CAST (Cognition After STroke) study, dementia and mild cognitive impairment (MCI) were diagnosed and sub-classified according to proposed underlying etiology at one- and seven-years post-stroke (38, 39). In the present sub-study from the CAST cohort, all stroke survivors were offered ^{18}F-Flut-PET at seven-year follow-up. To our knowledge, this is the first study on ^{18}F-Flut-PET seven years post-stroke.

We hypothesized that amyloid deposition is common in stroke survivors diagnosed with CI and, further, that quantitatively assessed ^{18}F-Flut-PET uptake at seven years post-stroke correlates with CSF Aβ□□ levels at one year, and with measures of neurodegeneration and cognition at seven years.

Methods

Participants

All patients with a first-ever stroke or TIA admitted to the stroke unit, at Bærum Hospital during 2007/2008 were invited to participate in the CAST study. Patients with subarachnoid hemorrhage, dementia or MCI diagnosed before the stroke, patients who did not speak Norwegian and patients with a remaining life expectancy of less than one year estimated by the treating physician were excluded. The Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE)(40) was answered by the patient´s spouse, a first-degree relative or a close friend. A score of ≥ 3.44 on the IQCODE indicated pre-stroke cognitive decline, and the patient was excluded. From February 2014 to July 2016, surviving participants were invited to participate in the present follow-up study.

Examinations and Assessments

At baseline, stroke etiology was classified according to the Trial of ORG 10172 (TOAST) classification (41), and patients underwent neuroimaging with computed tomography (CT) and/or magnetic resonance imaging (MRI).

In short, at baseline, one and seven-year, vascular risk factors and current medication were recorded. Fasting blood samples, electrocardiography (ECG) and weight and height were measured, with calculation of body mass index (BMI). Neurological impairment was assessed using the National Institutes of Health Stroke Scale (NIHSS) (42). Cognitive evaluation included the Mini Mental State Examination (MMSE)(43), the clock drawing test (44), the Trail making test A and B (TMT-A and B) (45), and the 10 word memory test (46). Additional tests at the seven year follow-up were the Montreal Cognitive Assessment (MoCA) (47) and Controlled Oral Word Association Test (COWA) (48). Global functional outcome was assessed by the modified Rankin Scale (mRS) (49) and personal activities of daily living (p-ADL) by the Barthel Activities of Daily Living Index (49).

Supplementary investigations at one and seven years included MRI of the brain, colour doppler of the precerebral arteries, and when possible, a lumbar puncture for examination of cerebrospinal fluid (CSF) biomarkers for neurodegenerative disease (amyloid-β peptide (Aβ□□) levels, total tau (T-tau) and phosphorylated tau (P-tau)) quantified with commercially available ELISAs (Fujirebio Europe, Gent, Belgium). CSF was collected in polypropylene tubes and immediately transported to the local laboratory, in accordance with the manufacturers' instructions. The laboratory recommended a cut-off value of Aβ□□≤ 550 ng/L for abnormality, modified from Sjögren et al (50).

Cerebral MRI

At one- and seven-years follow-up, MRI scans were acquired on a Philips Intera system 1.5 T (Philips Medical Systems, Best, The Netherlands). The MRI study protocol consisted of 3D-T1, axial T2, 3D-FLAIR, DWI and SWI sequences

MRI investigations were evaluated for focal vascular lesions, medial temporal lobe atrophy (MTLA), white matter lesions (WML), and global cortical atrophy (GCA), by two radiologists, blinded to the clinical information. Any discrepancies were resolved by consensus. MTLA was graded from 0 to 4; with MTLA grade 0 = no atrophy, MTLA 4 = highest degree of atrophy. MTLA 0–1 is considered normal (51). WML was rated using the visual rating scale proposed by Fazekas, scores ranging from 0 to 3 (52). GCA was rated using the visual rating scale known as Pasquier scale, ranging from 0 to 3 (53).

MRI Segmentations and Analyses

□Cortical reconstruction and volumetric segmentation were performed with the FreeSurfer image analysis suite version 6.0.0 (http://surfer.nmr.mgh. harvard.edu/). This includes segmentation of the subcortical white-matter and deep gray-matter volumetric structures (54) and parcellation of the cortical surface (55). This labels cortical sulci and gyri, and thickness values are calculated in the regions of interest. All segmentations were manually inspected.

^{18} F-Flutemetamol PET CT acquisition

At seven years follow-up, patients were examined with a Siemens Biograph40 mCT scanner (Siemens Healthineers, Erlangen, Germany). All patients received an intravenous injection of approximately 185 MBq ^{18}F-Flutemetamol (mean 188 MBq, range 165–218). Image acquisition started approximately 90 minutes after

injection (mean 91 minutes, range 78–108) with a low dose CT followed by PET acquisition for 20 minutes (four frames of five minutes). 3D dynamic emission data were obtained with a resolution recovery algorithm with time of flight (TrueX with two iterations, 21 subsets and a Gaussion filter with FWHM of 2 mm, matrix size 400 × 400). Reconstructed images had a slice thickness of 2 mm and a voxel size of $2 \times 2 \times 2$ mm^3.

Qualitative classification of ^{18}F-Flutemetamol PET

^{18}F-Flut PET images were visually classified as positive (^{18}F-Flut-PET (+)) or negative (^{18}F-Flut-PET (-)) by at least two nuclear medicine physicians with experience in ^{18}F-Flut PET, and recorded in patients' medical records in line with standard clinical practice between 2015–2017. In addition one nuclear medicine physician with experience in ^{18}F-Flut PET repeated classification in 2019, and in case of discrepancy between the classifications, an additional expert was consulted. All image classifications were performed according to the validated electronic reader programme (56) and as described previously (14).

Quantitative classification of ^{18}F-Flutemetamol PET

Motion correction of the ^{18}F-Flut PET was performed using frame-by-frame rigid registration, then the frames were summed to a single time-frame image and rigidly registered to the anatomical MRI volume using a 6-parameter rigid registration as implemented in the Statistical Parametrical Mapping (SPM 12, Wellcome Trust Centre for Neuroimaging, UCL, UK) toolbox. ^{18}F-Flut-PET standardized uptake value ratios (SUVr) were obtained by normalization to the pons. Prior to normalization, the brainstem mask was eroded by 1 mm to avoid partial volume effects, inaccurate segmentation or co-registration. ^{18}F-Flut-PET uptake was analyzed in five pre-selected cortical regions of interest (ROIs), as defined by Desikan et al. (57) and implemented in FreeSurfer as described above, known to hold substantial amyloid plaques in AD: the precuneus and posterior cingulate combined, anterior cingulate, prefrontal, inferior parietal, and lateral temporal cortex (58). The ^{18}F-Flut-PET uptake for each region was averaged across the hemispheres. We further calculated a composite SUVr by averaging the uptake in the above-mentioned regions.

Outcomes and Diagnosis of cognitive function

At one and seven years post-stroke, the diagnoses of dementia and MCI were made in consensus meetings by two senior neurologists (B.F and B.T) and one senior geriatrician (A.R.Ø), using the criteria outlined by Winblad et al. (59) for MCI, and the International Classification of Diseases 10th revision (ICD-10) criteria (60) for dementia. Details of the novel method for sub-classification have previously been reported (39), with six potential subgroups; degenerative MCI or degenerative dementia, vascular MCI (MCI VaD) or vascular dementia (dementia VaD) or mixed degenerative and vascular MCI or dementia. The evaluations were based on the results from the medical history, cognitive assessments, the IQCODE and information regarding daily functioning. Sub-classification for proposed underlying etiology was based on MRI findings of vascular or degenerative brain changes, biomarkers in the CSF, the patient´s vascular risk factors and clinical cognitive profile. Patients were classified with possible vascular disease when the radiological findings revealed WMLs without MTLA, while MTLA without WMLs was interpreted as degenerative etiology. Patients with combined pathologies were classified with mixed vascular and degenerative disease.

Statistics

Baseline, one- and seven-years characteristics are given as mean ± standard deviation (SD) or as numbers and percentages as appropriate. Categorical variables were compared with Pearson's chi-squared test and continuous variables with independent Student t-test. The relationship between death as dependent variable and age-adjusted CSF as independent variables were assessed with logistic regression analyses. Correlation analyses of ^{18}F-Flut-PET SUVr and measures of neurodegeneration and cognition, were performed assessing the Pearson correlation coefficient in continuous variables (MTA, CSF Aβ levels, GCA, TMT-A), Spearman rho in ranked data (MMSE). Linear regression analyses were performed with ^{18}F-Flut-PET SUVr as explanatory variable. Each regression model was adjusted for age. Statistical analyses were performed using SPSS Statistic version 23.

Results

Study population

Of the 208 patients included in 2007–2008, 111 completed seven years follow-up, of whom 26 patients agreed to PET imaging and13 of these had CSF from 12 months. In total, 80 patients died during the study period, and 17 were lost to follow-up for other reasons. A flow chart is presented in Fig. 1. Characteristics and assessments at baseline and seven years for the complete study population are presented in Table 1. Characteristics and assessment at baseline, clinical cognitive profile and MRI findings at one year in stroke survivors by PET or no PET at seven years are presented in Table 2. Significantly more patients who agreed to PET had normal cognition and lower CSF T-tau at 12 months follow-up. There were no differences regarding age, stroke subtype or assessments at baseline, or MRI findings at one year.

Table 1

Baseline characteristics (n = 208) and assessments in survivors at seven years (n = 111)

	Baseline	7 year follow-up
Male (%)	105 (51)	61 (55)
Mean age, years (SD)	72.0 (12.2)	75.2 (11.2)
Less than 9 years of education (%)	50 (24)	1.02 (2.3) (109)
Stroke subtype (%)	164 (79)	18.7 (3.7) (109)
Cerebral infarction	28 (14)	1.4 (1.3) (109)
TIA	16 (7)	25.8 (5.9) (n = 109)
Cerebral haemorrhage	123 (59)	55.7 (39.6) (n = 101)
Risk factors (%)	117 (56)	126.4 (67.7) (n = 82)
Hypertension*	23 (11)	22.5 (8) (n = 106)
Hyperlipidemia	18 (18)	4.7 (3) (n = 105)
Diabetes	45 (22)	
Cigarette smoking (present)	65 (31)	
Coronary heart disease	20 (24)	
Atrial fibrillation	119 (57)	
Daily alcohol use	21 (10)	
BMI > 25	60 (29)	
TOAST classification (%)	64 (31)	
Large-vessel disease	63 (30)	
Cardio-embolic disease	2.44 (4.6)	
Small-vessel disease	17.5 (5.1)	
Stroke of undetermined aetiology	1.5 (1.4)	
Assessments. Mean (SD) (n)	3.1 (0.2) (n = 208)	
NIHSS	26.0 (4.5) (n = 195)	
BI	73.7 (66.7) (n = 177)	
mRS	152.8 (89.8) (n = 152)	
IQCODE	17.9 (2.9) (n = 170)	
MMSE	4.3 (2.5) (n = 184)	
TMT-A		
TMT-B		
10-Word test immediate recall		
10-Word test, delayed recall		

TIA = Transistent Ischemic Attack; Hyperlipidemia = total cholesterol > 5 mmol/L or LDL > 3 mmol/L; LDL = Low Density Lipoprotein; Diabetes = an established diagnosis or Haemoglobin A1C (HbA1c) ≥ 7.0; Coronary Heart Disease = previous myocardial infarction or present angina pectoris; BMI = Body mass index; TOAST = the trial of org 10172 in acute stroke treatment classification; NIHSS = National Institute of Health Stroke Scale; BI = Barthel Activities of Daily Living Index; mRS = modified Rankin scale; IQCODE = the informant questionnaire on cognitive decline in the elderly. MMSE = Mini Mental State Examination; SD = standard deviation.* Hypertension = use of BP lowering drugs at baseline.

Table 2

Characteristics at baseline, clinical cognitive profile and MRI findings at one year in stroke survivors by PET or no PET at seven years.

	PET	NO PET	P value
N	26	85	0.227
Male (%)	18 (69)	43 (51)	0.239
Mean age, years (SD)	72.9 (7.0)	75.9 (11.8)	0.776
Less than 9 years of education (%)	4 (15)	18 (21)	0.288
Living alone (%)	4 (15)	24 (28)	0.926
Stroke subtype (%)	20 (77)	66 (78)	0.724
Cerebral infarction	4 (15)	11 (13)	0.247
TIA	2 (8)	8 (9)	0.266
Cerebral haemorrhage	2 (8)	12 (14)	0.641
TOAST classification (%)	8 (31)	19 (22)	0.113
Large-vessel disease	9 (35)	29 (34)	0.223
Cardio-embolic disease	7 (27)	25 (30)	0.286
Small-vessel disease	1.12 (2.1)(26)	1.99 (3.6)(85)	0.040
Stroke of undetermined aetiology	1.0 (1.2)(26)	1.26 (1.2)(85)	0.135
Assessments. Mean (SD) (n)	3.0 (0.1)(26)	3.1 (0.2)(85)	0.095
NIHSS	27.8 (2.1)(26)	26.5 (4.0)(82)	0.177
mRS	1 (25)	13 (84)	0.824
IQCODE	6 (25)	31 (84)	0.040
MMSE	19 (25)	40 (84)	
Clinical profile 12 months	0.79 (0.8)(24)	1.18 (1.2)(77)	
Dementia	1.52 (0.8)(25)	1.86 (0.9)(76)	
MCI	1.28 (0.7)(25)	1.48 (0.6)(75)	
Normal cognition	840 (250) (13)	861(302) (41)	
MRI 12 months. Mean (SD) (n)	270 (101)(13)	387(192) (41)	
MTLA grade			
Fazekas score			
Global Cortical Atrophy			
CSF (Aβ)-42 (ng/L) 12 months (n)			
CSF total tau (ng/L) 12 months (n)			

TIA = Transient Ischemic Attack; TOAST = the trial of org 10172 in acute stroke treatment classification; NIHSS = National Institute of Health Stroke Scale; BI = Barthel Activities of Daily Living Index; mRS = modified Rankin scale; IQCODE = the informant questionnaire on cognitive decline in the elderly; MMSE = Mini Mental State Examination; SD = standard deviation;MCI = mild cognitive impairment; MTLA = medial temporal lobe atrophy. CSF (Aβ)-42 = cerebrospinal fluid amyloid-β peptide

Amyloid binding in stroke survivors

The main characteristics, MRI, ^{18}F-Flut-PET, and cognitive assessment findings are summarized in Table 3 (see Additional file 1). Among the 26 patients who agreed to PET, five patients had no MRI at seven years, required in our quantitative assessment method. Four scans were visually classified ^{18}F-Flut(+). 13 patients were diagnosed with CI (mixed or neurodegenerative disease) at seven years, one with a positive PET scan. Quantitative ^{18}F-Flut-PET SUVr in different cortical regions is presented in Table 4.

Table 4

Quantitative ^{18}F-Flutemetamol PET SUVr in different cortical regions

Cases	precuneus and posterior cingulate combined	anterior cingulate	prefrontal	inferior parietal	lateral temporal	Composite SUVr
1	-	-	-	-	-	0.65
2	-	-	-	-	-	0.50
3	0.82	0.70	0.60	0.64	0.55	0.57
4	-	-	-	-	-	0.54
5	0.48	0.47	0.46	0.46	0.44	0.55
6	0.55	0.56	0.52	0.51	0.51	0.74
7	0.54	0.48	0.48	0.48	0.48	0.54
8	0.54	0.52	0.50	0.51	0.49	1.13
9	0.85	0.68	0.68	0.75	0.65	0.55
10	-	-	-	-	-	0.53
11	0.52	0.51	0.49	0.49	0.48	0.57
12	1.24	1.21	1.21	1.14	1.16	0.63
13	0.54	0.49	0.50	0.51	0.49	0.58
14	-	-	-	-	-	0.52
15	0.51	0.48	0.47	0.49	0.47	0.49
16	0.57	0.54	0.51	0.53	0.50	0.51
17	0.64	0.64	0.56	0.59	0.57	0.54
18	0.59	0.63	0.57	0.53	0.51	0.50
19	0.51	0.50	0.46	0.47	0.46	0.53
20	0.48	0.45	0.44	0.45	0.43	0.59
21	0.50	0.48	0.46	0.46	0.46	0.54
22	0.51	0.47	0.48	0.49	0.50	
23	0.49	0.49	0.48	0.48	0.47	
24	0.51	0.50	0.47	0.46	0.48	
25	0.56	0.53	0.57	0.50	0.53	
26	0.54	0.54	0.51	0.48	0.50	

Comparing patients according to normal or CI at seven years, no difference in mean SUVr (SD) was observed (0.57 (0.08) vs 0.60 (0.18), p = 0.54). Eight patients changed from normal cognition at one year to CI at seven years, one of whom was amyloid positive. When comparing cognitive decline to stable cognition during follow-up, no difference in mean SUVr (SD) was observed (0.65 (0.24) vs 0.56 (0.07), p = 0.16). Three of four patients with visually positive PET had normal cognition at seven years.

80 patients died before follow-up, 33 with CSF from one year. Logistic regression assessing age-adjusted CSF Aβ□□ levels and death, did not demonstrate any significant association (OR 1.0, 95%CI 0.99-1.0). No significant association was seen between age-adjusted CSF Aβ□□ as a dichotomous variable, cutoff < 550 ng/L, and death (OR 1.3, 95%CI 0.24–7.48). Age adjusted CSF T-tau was not significantly associated with death (OR 1.0, 95%CI 1.0–1.0)

Correlations

^{18}F-Flut-PET SUVr at seven years did not correlate with CSF Aβ□□ levels at one year (r = 0.12; p = 0.703), MTLA (r = 0.10; p = 0.670), GCA (r = 0.10; p = 0.652) or MMSE (r=-0.32; p = 0.162) at seven years, when adjusted for age. TMT-A at seven years was significantly correlated to ^{18}F-Flut-PET SUVr (r = 0.69; p = 0.00), but exploring data revealed one outlier on scatterplot, and after exclusion, there were no significant correlation. Associations between composite ^{18}F-Flut-PET SUVr and CSF Aβ□□ levels at one year are presented in Fig. 2.

Discussion

In this cohort, only one patient diagnosed with CI seven years post stroke was amyloid positive. Quantitatively assessed ^{18}F-Flut-PET did not correlate with amyloid-β peptide (Aβ□□) levels in CSF at one year or MTLA, GCA, MMSE, or TMT-A at seven years.

Our findings with only one visually ^{18}F-Flut(+) in post-stroke CI patients (8%) are in line with the findings from the prospective DEDEMAS study (Determinants of Dementia After stroke), where only 2 out of 38 (5%) post-stroke MCI patients had positive amyloid scans. In the DEDEMAS study, neuropsychological testing was performed six months after stroke, and this might theoretically be too early to capture amyloid deposition initiated by the stroke. Long-term follow-up studies are needed, as the DEDEMAS authors also conclude. As in our study only a minor portion of patients completed the PET examination (38/178) (35). In our study more patients receiving amyloid PET had normal cognition at one year, implying that our results may be considered less representative for stroke survivors in general. Visual classification of ^{18}F-Flut-PET is still the only validated method for clinical use, however quantification is beneficial to obtain a continuous measure of ^{18}F-Flut-PET. One proposed cut-off for quantitatively assessed ^{18}F-Flut-PET using CortexID, with pons as reference region, is SUVr 0.61 (61). All patients with visually positive PET in our study had composite SUVr > 0.61 in line with the cut-off, even though we applied a different software for quantification.

Roberts et al studied the prevalence of PET amyloid-positivity in a non-demented cohort drawn from the general population, and found that amyloid positivity in persons with MCI ranged from 0% in the age group 50–59 to 16% in participants aged 80–89 years (11). Previous studies have reported a slightly higher prevalence between 10 and 30% in cognitively healthy-people (62, 63). The frequency of amyloid positivity in our cohort is consistent with the observations from the general population, so no evident stroke-related inflammation with amyloid deposition is observed in our cases. Two cases had larger strokes with NIHSS ≥ 4 at discharge, both without amyloid positivity after seven years. When assessing PET semi- quantitatively, PET SUVr did not differ substantially between cases, and there was no significant difference when comparing those with or without CI, or when comparing those who experienced cognitive decline or stable cognition during follow-up. Three patients were diagnosed with MCI AD in consensus, proposing neurodegenerative disease as dominating pathology. None had amyloid positivity. This is in line with a previous study from the CAST cohort, where we found a correlation between pathological cerebrospinal fluid (CSF) concentrations of microtubule-associated protein tau (T-tau) one year post-stoke and brain atrophy, indicating that tau-linked neurodegeneration might be more important than amyloid post-stroke (64). Recent studies suggest that changes in the blood-brain barrier (BBB) and BBB-mediated neurodegeneration, plays an important role in cognitive dysfunction independent of Aβ biomarkers (65, 66).

In the study by Roberts et al, more amyloid-positive participants without cognitive impairment died compared to amyloid negative during the four year follow-up period, 13% vs 4.6% respectively (11). Death before follow-up might bias our findings, but when assessing the relation between CSF biomarkers at one year and prospective mortality using logistic regression analysis, CSF Aβ□□ at one year was not associated with death in our cohort.

As shown in Fig. 2, surprisingly, CSF Aβ□□ at one year did not correlate with PET SUVr at seven years. Three patients had pathological levels of CSF Aβ□□ at one year, all without amyloid positivity at seven years. CSF Aβ□□ decreases to pathological levels before amyloid PET (67, 68), and thus this may be of importance in clinical

diagnostic routine. Contrary to CSF T-tau, CSF Aβ□□ levels remain unchanged after stroke when followed for six months (69). One possible explanation could be that stroke decreases the ability to amyloid clearance, maybe due to changes in the blood-brain barrier (BBB) (70), with normalization after some years. Garcia-Alloza et al (71) demonstrated Aβ formation in a mice model as a transient phenomenon induced by a stroke, most likely through interference with amyloid clearance pathways. One study with repeated amyloid PET in 21 patients, one and 18 month post-stroke, found a significant reduction in amyloid accumulation in the infarct region, probably caused by a breakdown of BBB in the acute phase, with leak of the radioactive ligand with “false” high SUVr (31). The optimal timing for Aβ assessment post-stroke is not known and needs to be explored in order to develop future prediction models and individualized management. Due to small numbers, our observations must be confirmed in lager samples, and interpreted with caution.

Our study has several limitations. First our limited sample size, as only 56 patients agreed to lumbar puncture at one year and 26 to PET after seven years. Patients on anticoagulation therapy or were unable to give consent were excluded from lumbar puncture due to ethical considerations, and thus might bias our findings. After seven years, only highly motivated patients due to time consuming examinations and long travel distances between hospitals, and more with normal cognition at one year, agreed to PET, making our findings less generalizable. The strength in our study is the long-term follow-up with the same team of nurses and physicians, and a measurement of amyloid at two time points. As far as we know, this is the first study to offer PET examination seven years post-stroke, and by that adding important knowledge to amyloid evaluation post-stroke. Studies have shown that plasma Aβ42/Aβ40 levels accurately determine amyloid PET status in cognitively normal research participants (72), and, therefore, might be more feasible in a post-stroke population, both due to antithrombotic medication, CI and low PET attendance in most studies so far.

Conclusions

In conclusion, amyloid binding was not common in our cohort of stroke survivors diagnosed with CI. Assessed quantitatively, amyloid load correlates neither with other measures related to neurodegeneration nor with CSF Aβ□□ at one year in this cohort. Therefore amyloid pathology may not be a key mediator of neurodegeneration seven years post-stroke. Our findings must be validated in lager studies.

Declarations

Ethics approval and consent to participate

The study was approved by the Regional Committee for Ethics (REK) in Medical Research and by the Data Protection Authorities (2013/1829). Written informed consent was obtained from all patients; if the patient was cognitively impaired, relatives also gave their written assent. Patients unable to give consent were excluded from lumbar puncture in line with recommendations from REK.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used during the current study are available from the corresponding author on reasonable request.

Competing interests

Hege Ihle-Hansen is a member of the editorial board in BMC neurology.

Funding

The authors work has been supported from Vestre Viken Hospital Trust.

Authors' contributions

BF, BT, ARØ, HelH, TBW and GH researched literature and conceived the study. HelH, BF, BT and GH were invoved in the protocol development and gaining ethical approval. HåIH, HelH and GH were involved in patient recruitment. GH wrote the first draft of the manuscript. All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Acknowledgements

Not applicable.

Abbreviations

AD Alzheimer’s disease

BMI body mass index

CAST Cognition After STroke

CI Cognitive impairment

COWA Controlled Oral Word Association Test

CSF Aβ□□ Amyloid-β peptide-42

CSF Cerebrospinal fluid

CT Computer tomography

ECG ECG

GCA Global cortical atrophy

IQCODE Informant Questionnaire on Cognitive Decline in the elderly

MCI Mild cognitive impairment

MMSE Mini Mental State Examination

MoCA Montreal Cognitive Assessment

MRI Magnetic resonance imaging

mRS Modified Rankin Scale

MTLA Medial temporal lobe atrophy

NIHSS National Institutes of Health Stroke Scale

OCSP Oxfordshire Community Stroke Project classification

p-ADL Barthel Activities of Daily Living Index

PET Positron emission tomography

P-tau Phosphorylated microtubule-associated protein tau

RCT Randomized controlled trial

SUVr standardized uptake value ratios

TIA Transitory ischemic attack

TOAST The Trial of Org 10,172 in Acute Stroke Treatment

TMT A Trail Making Test A

TMT B Trail Making Test B

T-tau Microtubule-associated protein tau

VaD Vascular

^{18}F-Flut ^{18}F-Flutemetamol

References

1. Brainin M, Tuomilehto J, Heiss WD, Bornstein NM, Bath PM, Teuschl Y, et al. Post-stroke cognitive decline: an update and perspectives for clinical research. European journal of neurology. 2015;22(2):229-38, e13-6.
2. Ballard C, Rowan E, Stephens S, Kalaria R, Kenny RA. Prospective follow-up study between 3 and 15 months after stroke: improvements and decline in cognitive function among dementia-free stroke survivors >75 years of age. Stroke; a journal of cerebral circulation. 2003;34(10):2440-4.
3. Rasquin SM, Lodder J, Verhey FR. Predictors of reversible mild cognitive impairment after stroke: a 2-year follow-up study. Journal of the neurological sciences. 2005;229-230:21-5.
4. Tang EY, Amiesimaka O, Harrison SL, Green E, Price C, Robinson L, et al. Longitudinal Effect of Stroke on Cognition: A Systematic Review. Journal of the American Heart Association. 2018;7(2).

5. Rothwell PM, Coull AJ, Giles MF, Howard SC, Silver LE, Bull LM, et al. Change in stroke incidence, mortality, case-fatality, severity, and risk factors in Oxfordshire, UK from 1981 to 2004 (Oxford Vascular Study). Lancet. 2004;363(9425):1925-33.
6. Kandiah N, Chander RJ, Lin X, Ng A, Poh YY, Cheong CY, et al. Cognitive Impairment after Mild Stroke: Development and Validation of the SIGNAL2 Risk Score. Journal of Alzheimer's disease : JAD. 2016;49(4):1169-77.
7. Chander RJ, Lam BYK, Lin X, Ng AYT, Wong APL, Mok VCT, et al. Development and validation of a risk score (CHANGE) for cognitive impairment after ischemic stroke. Scientific reports. 2017;7(1):12441.
8. Yang J, Wong A, Wang Z, Liu W, Au L, Xiong Y, et al. Risk factors for incident dementia after stroke and transient ischemic attack. Alzheimer's & dementia : the journal of the Alzheimer's Association. 2015;11(1):16-23.
9. Liu W, Wong A, Au L, Yang J, Wang Z, Leung EY, et al. Influence of Amyloid-beta on Cognitive Decline After Stroke/Transient Ischemic Attack: Three-Year Longitudinal Study. Stroke; a journal of cerebral circulation. 2015;46(11):3074-80.
10. Lopez OL, Klunk WE, Mathis C, Coleman RL, Price J, Becker JT, et al. Amyloid, neurodegeneration, and small vessel disease as predictors of dementia in the oldest-old. Neurology. 2014;83(20):1804-11.
11. Roberts RO, Aakre JA, Kremers WK, Vassilaki M, Knopman DS, Mielke MM, et al. Prevalence and Outcomes of Amyloid Positivity Among Persons Without Dementia in a Longitudinal, Population-Based Setting. JAMA Neurol. 2018;75(8):970-9.
12. van Maurik IS, van der Kall LM, de Wilde A, Bouwman FH, Scheltens P, van Berckel BNM, et al. Added value of amyloid PET in individualized risk predictions for MCI patients. Alzheimer's & dementia (Amsterdam, Netherlands). 2019;11:529-37.
13. Leuzy A, Savitcheva I, Chiotis K, Lilja J, Andersen P, Bogdanovic N, et al. Clinical impact of [(18)F]flutemetamol PET among memory clinic patients with an unclear diagnosis. European journal of nuclear medicine and molecular imaging. 2019;46(6):1276-86.
14. Muller EG, Edwin TH, Stokke C, Navelsaker SS, Babovic A, Bogdanovic N, et al. Amyloid-beta PET-Correlation with cerebrospinal fluid biomarkers and prediction of Alzheimer s disease diagnosis in a memory clinic. PloS one. 2019;14(8):e0221365.
15. Blennow K, Hampel H, Weiner M, Zetterberg H. Cerebrospinal fluid and plasma biomarkers in Alzheimer disease. Nature reviews Neurology. 2010;6(3):131-44.
16. Perani D, Schillaci O, Padovani A, Nobili FM, Iaccarino L, Della Rosa PA, et al. A survey of FDG- and amyloid-PET imaging in dementia and GRADE analysis. BioMed research international. 2014;2014:785039.
17. Ikonomovic MD, Fantoni ER, Farrar G, Salloway S. Infrequent false positive [(18)F]flutemetamol PET signal is resolved by combined histological assessment of neuritic and diffuse plaques. Alzheimer's research & therapy. 2018;10(1):60.
18. Zhang S, Smailagic N, Hyde C, Noel-Storr AH, Takwoingi Y, McShane R, et al. (11)C-PIB-PET for the early diagnosis of Alzheimer's disease dementia and other dementias in people with mild cognitive impairment (MCI). The Cochrane database of systematic reviews. 2014;7:Cd010386.
19. Palmqvist S, Zetterberg H, Blennow K, Vestberg S, Andreasson U, Brooks DJ, et al. Accuracy of brain amyloid detection in clinical practice using cerebrospinal fluid beta-amyloid 42: a cross-validation study against

amyloid positron emission tomography. JAMA Neurol. 2014;71(10):1282-9.

20. Adamczuk K, Schaeverbeke J, Vanderstichele HM, Lilja J, Nelissen N, Van Laere K, et al. Diagnostic value of cerebrospinal fluid Abeta ratios in preclinical Alzheimer's disease. Alzheimer's research & therapy. 2015;7(1):75.
21. Hansson O, Seibyl J, Stomrud E, Zetterberg H, Trojanowski JQ, Bittner T, et al. CSF biomarkers of Alzheimer's disease concord with amyloid-beta PET and predict clinical progression: A study of fully automated immunoassays in BioFINDER and ADNI cohorts. Alzheimer's & dementia : the journal of the Alzheimer's Association. 2018;14(11):1470-81.
22. Whitehead S, Cheng G, Hachinski V, Cechetto DF. Interaction between a rat model of cerebral ischemia and beta-amyloid toxicity: II. Effects of triflusal. Stroke; a journal of cerebral circulation. 2005;36(8):1782-9.
23. Whitehead SN, Hachinski VC, Cechetto DF. Interaction between a rat model of cerebral ischemia and beta-amyloid toxicity: inflammatory responses. Stroke; a journal of cerebral circulation. 2005;36(1):107-12.
24. Amtul Z, Nikolova S, Gao L, Keeley RJ, Bechberger JF, Fisher AL, et al. Comorbid Abeta toxicity and stroke: hippocampal atrophy, pathology, and cognitive deficit. Neurobiology of aging. 2014;35(7):1605-14.
25. Thiel A, Cechetto DF, Heiss WD, Hachinski V, Whitehead SN. Amyloid burden, neuroinflammation, and links to cognitive decline after ischemic stroke. Stroke; a journal of cerebral circulation. 2014;45(9):2825-9.
26. Leys D, Henon H, Mackowiak-Cordoliani MA, Pasquier F. Poststroke dementia. The Lancet Neurology. 2005;4(11):752-9.
27. Fein G, Di Sclafani V, Tanabe J, Cardenas V, Weiner MW, Jagust WJ, et al. Hippocampal and cortical atrophy predict dementia in subcortical ischemic vascular disease. Neurology. 2000;55(11):1626-35.
28. Lee JH, Kim SH, Kim GH, Seo SW, Park HK, Oh SJ, et al. Identification of pure subcortical vascular dementia using 11C-Pittsburgh compound B. Neurology. 2011;77(1):18-25.
29. Selnes P, Grambaite R, Rincon M, Bjornerud A, Gjerstad L, Hessen E, et al. Hippocampal complex atrophy in poststroke and mild cognitive impairment. Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism. 2015;35(11):1729-37.
30. Gorelick PB, Scuteri A, Black SE, Decarli C, Greenberg SM, Iadecola C, et al. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the american heart association/american stroke association. Stroke; a journal of cerebral circulation. 2011;42(9):2672-713.
31. Sahathevan R, Linden T, Villemagne VL, Churilov L, Ly JV, Rowe C, et al. Positron Emission Tomographic Imaging in Stroke: Cross-Sectional and Follow-Up Assessment of Amyloid in Ischemic Stroke. Stroke; a journal of cerebral circulation. 2016;47(1):113-9.
32. Yasuno F, Kajimoto K, Ihara M, Taguchi A, Yamamoto A, Fukuda T, et al. Amyloid beta deposition in subcortical stroke patients and effects of educational achievement: A pilot study. International journal of geriatric psychiatry. 2019.
33. Pendlebury et al (in press 2020)
34. Gottesman RF, Schneider AL, Zhou Y, Coresh J, Green E, Gupta N, et al. Association Between Midlife Vascular Risk Factors and Estimated Brain Amyloid Deposition. Jama. 2017;317(14):1443-50.
35. Wollenweber FA, Darr S, Muller C, Duering M, Buerger K, Zietemann V, et al. Prevalence of Amyloid Positron Emission Tomographic Positivity in Poststroke Mild Cognitive Impairment. Stroke; a journal of cerebral circulation. 2016;47(10):2645-8.

36. Mok V, Leung EY, Chu W, Chen S, Wong A, Xiong Y, et al. Pittsburgh compound B binding in poststroke dementia. Journal of the neurological sciences. 2010;290(1-2):135-7.
37. Mok V, Xiong Y, Wong KK, Wong A, Schmidt R, Chu WW, et al. Predictors for cognitive decline in patients with confluent white matter hyperintensities. Alzheimer's & dementia : the journal of the Alzheimer's Association. 2012;8(5 Suppl):S96-s103.
38. Hagberg G, Fure B, Thommessen B, Ihle-Hansen H, Oksengard AR, Nygard S, et al. Predictors for Favorable Cognitive Outcome Post-Stroke: A-Seven-Year Follow-Up Study. Dementia and geriatric cognitive disorders. 2019:1-11.
39. Ihle-Hansen H, Thommessen B, Wyller TB, Engedal K, Oksengard AR, Stenset V, et al. Incidence and subtypes of MCI and dementia 1 year after first-ever stroke in patients without pre-existing cognitive impairment. Dementia and geriatric cognitive disorders. 2011;32(6):401-7.
40. Jorm AF, Scott R, Cullen JS, MacKinnon AJ. Performance of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) as a screening test for dementia. Psychological medicine. 1991;21(3):785-90.
41. Adams HP, Jr., Biller J. Classification of subtypes of ischemic stroke: history of the trial of org 10172 in acute stroke treatment classification. Stroke; a journal of cerebral circulation. 2015;46(5):e114-7.
42. Goldstein LB, Bertels C, Davis JN. Interrater reliability of the NIH stroke scale. Archives of neurology. 1989;46(6):660-2.
43. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. Journal of psychiatric research. 1975;12(3):189-98.
44. Eddy JR, Sriram S. Clock-drawing and telling time as diagnostic aids. Neurology. 1977;27(6):595.
45. RM R. Validity of the trail making test as an indicator of organic brain damage. Percept Mot Skills. 1958;8:271-6.
46. Randolph C, Tierney MC, Mohr E, Chase TN. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): preliminary clinical validity. Journal of clinical and experimental neuropsychology. 1998;20(3):310-9.
47. Nasreddine ZS, Phillips NA, Bedirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. Journal of the American Geriatrics Society. 2005;53(4):695-9.
48. Barry D, Bates ME, Labouvie E. FAS and CFL forms of verbal fluency differ in difficulty: a meta-analytic study. Applied neuropsychology. 2008;15(2):97-106.
49. Sulter G, Steen C, De Keyser J. Use of the Barthel index and modified Rankin scale in acute stroke trials. Stroke; a journal of cerebral circulation. 1999;30(8):1538-41.
50. Sjogren M, Vanderstichele H, Agren H, Zachrisson O, Edsbagge M, Wikkelso C, et al. Tau and Abeta42 in cerebrospinal fluid from healthy adults 21-93 years of age: establishment of reference values. Clinical chemistry. 2001;47(10):1776-81.
51. Scheltens P, Weinstein HC, Leys D. Neuro-imaging in the diagnosis of Alzheimer's disease. I. Computer tomography and magnetic resonance imaging. Clinical neurology and neurosurgery. 1992;94(4):277-89.
52. Pantoni L, Basile AM, Pracucci G, Asplund K, Bogousslavsky J, Chabriat H, et al. Impact of age-related cerebral white matter changes on the transition to disability -- the LADIS study: rationale, design and

methodology. Neuroepidemiology. 2005;24(1-2):51-62.

53. Pasquier F, Leys D, Weerts JG, Mounier-Vehier F, Barkhof F, Scheltens P. Inter- and intraobserver reproducibility of cerebral atrophy assessment on MRI scans with hemispheric infarcts. European neurology. 1996;36(5):268-72.
54. Fischl B, Salat DH, Busa E, Albert M, Dieterich M, Haselgrove C, et al. Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. Neuron. 2002;33(3):341-55.
55. Chincarini A, Peira E, Morbelli S, Pardini M, Bauckneht M, Arbizu J, et al. Semi-quantification and grading of amyloid PET: A project of the European Alzheimer's Disease Consortium (EADC). NeuroImage Clinical. 2019;23:101846.
56. Buckley CJ, Sherwin PF, Smith AP, Wolber J, Weick SM, Brooks DJ. Validation of an electronic image reader training programme for interpretation of [18F]flutemetamol beta-amyloid PET brain images. Nuclear medicine communications. 2017;38(3):234-41.
57. Desikan RS, Segonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, et al. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. NeuroImage. 2006;31(3):968-80.
58. Thal DR, Attems J, Ewers M. Spreading of amyloid, tau, and microvascular pathology in Alzheimer's disease: findings from neuropathological and neuroimaging studies. Journal of Alzheimer's disease : JAD. 2014;42 Suppl 4:S421-9.
59. Winblad B, Palmer K, Kivipelto M, Jelic V, Fratiglioni L, Wahlund LO, et al. Mild cognitive impairment–beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. Journal of internal medicine. 2004;256(3):240-6.
60. Organization WH. The ICD-10 Classification of Mental and Behavioural Disorders: diagnostic criteria for research. Geneva. 1993.
61. Thurfjell L, Lilja J, Lundqvist R, Buckley C, Smith A, Vandenberghe R, et al. Automated quantification of 18F-flutemetamol PET activity for categorizing scans as negative or positive for brain amyloid: concordance with visual image reads. Journal of nuclear medicine : official publication, Society of Nuclear Medicine. 2014;55(10):1623-8.
62. Petersen RC, Wiste HJ, Weigand SD, Rocca WA, Roberts RO, Mielke MM, et al. Association of Elevated Amyloid Levels With Cognition and Biomarkers in Cognitively Normal People From the Community. JAMA Neurol. 2016;73(1):85-92.
63. Jansen WJ, Ossenkoppele R, Knol DL, Tijms BM, Scheltens P, Verhey FR, et al. Prevalence of cerebral amyloid pathology in persons without dementia: a meta-analysis. Jama. 2015;313(19):1924-38.
64. Logallo N, Novotny V, Assmus J, Kvistad CE, Alteheld L, Ronning OM, et al. Tenecteplase versus alteplase for management of acute ischaemic stroke (NOR-TEST): a phase 3, randomised, open-label, blinded endpoint trial. The Lancet Neurology. 2017;16(10):781-8.
65. Nation DA, Sweeney MD, Montagne A, Sagare AP, D'Orazio LM, Pachicano M, et al. Blood-brain barrier breakdown is an early biomarker of human cognitive dysfunction. Nature medicine. 2019;25(2):270-6.
66. Zhao Z, Nelson AR, Betsholtz C, Zlokovic BV. Establishment and Dysfunction of the Blood-Brain Barrier. Cell. 2015;163(5):1064-78.

67. Cairns NJ, Ikonomovic MD, Benzinger T, Storandt M, Fagan AM, Shah AR, et al. Absence of Pittsburgh compound B detection of cerebral amyloid beta in a patient with clinical, cognitive, and cerebrospinal fluid markers of Alzheimer disease: a case report. Archives of neurology. 2009;66(12):1557-62.
68. Palmqvist S, Mattsson N, Hansson O. Cerebrospinal fluid analysis detects cerebral amyloid-beta accumulation earlier than positron emission tomography. Brain : a journal of neurology. 2016;139(Pt 4):1226-36.
69. Hesse C, Rosengren L, Vanmechelen E, Vanderstichele H, Jensen C, Davidsson P, et al. Cerebrospinal fluid markers for Alzheimer's disease evaluated after acute ischemic stroke. Journal of Alzheimer's disease : JAD. 2000;2(3-4):199-206.
70. Tarasoff-Conway JM, Carare RO, Osorio RS, Glodzik L, Butler T, Fieremans E, et al. Clearance systems in the brain-implications for Alzheimer disease. Nature reviews Neurology. 2015;11(8):457-70.
71. Garcia-Alloza M, Gregory J, Kuchibhotla KV, Fine S, Wei Y, Ayata C, et al. Cerebrovascular lesions induce transient beta-amyloid deposition. Brain : a journal of neurology. 2011;134(Pt 12):3697-707.
72. Schindler SE, Bollinger JG, Ovod V, Mawuenyega KG, Li Y, Gordon BA, et al. High-precision plasma beta-amyloid 42/40 predicts current and future brain amyloidosis. Neurology. 2019.

Table 3

3. Clinical characteristics, imaging features and CSF Aβ-42 of patients with PET examination

Age/ Gender	Stroke types/ Infract location/ NIHSS discharge	Cognitive evaluation		MTA	GCA	MSSE	TMT-A	Amyloid	Binding Year 7	CSF (Aβ)-42 (ng/L)
								Visual assessment	Semi-quantitative assessment	
Baseline		Year 1	Year 7	Year 7	Year 7	Year 7	Year 7	^{18}F-Flut(+)	Composite SUVr, max	Year 1
59 f	Cortical, left	Dementia	Normal	-	-	27	68	No	*	402
69 m	side, NIHSS 4	VaD	MCI	-	-	29	71	No	*	-
70 m	Lacunar, left	Normal	VaD	3.5	2	28	44	Yes	0.65, 0.82	-
73 m	side, NIHISS 0	Normal	Normal	-	-	30	37	No	*	-
73 f	Lacunar,	Normal	Normal	3.0	2	27	72	No	0.50, 0.65	-
63 m	posterior,	MCI mix	MCI	1.0	1	26	61	No	0.57, 0.76	1084
58 m	NIHSS 0	MCI mix	mix	1.5	1	27	32	No	0.54, 0.71	402
63 m	Lacunar, right	Normal	MCI	2.5	1	29	30	No	0.55, 0.69	985
68 m	side, NHISS 0	Normal	VaD	0.5	1	30	41	Yes	0.74, 0.85	-
73 m	TIA, right side,	Normal	MCI	-	-	29	48	Yes	*	-
65 m	NHISS 0	Normal	VaD	1.0	2	29	35	No	0.54, 0,71	804
78 f	Cortical, right	Normal	Normal	3.5	2	27	93	Yes	1.13, 1.24	-
71 m	side, NIHSS	Normal	Normal	2.0	1	28	29	No	0.55, 0.72	1171
74 m	10	Normal	Normal	-	-	28	37	No	*	-
58 m	Cortical, right	Normal	MCI	1.1	1	27	31	No	0.53, 0.71	848
50 m	side, NHISS 2	Normal	mix	0.5	1	28	24	No	0.57, 0.73	1175
61 m	Lacunar,	Normal	MCI	1.5	2	26	50	No	0.63, 0.79	-
66 f	posterior,	Normal	mix	1.0	1	27	43	No	0.58, 0.71	484
62 f	NIHSS 0	MCI mix	MCI	1.0	1	29	28	No	0.52, 0.70	-
64 f	Cortical, left	Normal	VaD	1.5	1	30	39	No	0.49, 0.64	761
72 m	side, NIHSS 0	Normal	MCI	0.5	2	29	30	No	0.51, 0.69	963
65 m	Undetermined,	MCI mix	AD	1.5	1	30	31	No	0.54, 0.72	825
52 f	left side,	Normal	MCI	1.0	1	29	26	No	0.50, 0.58	-
65 m	NIHSS 2	Normal	mix	1.5	1	28	30	No	0.53, 0.71	-
59 m	TIA, left side,	MCI mix	Normal	1.0	1	28	33	No	0.59, 0.77	901
70 f	NIHSS 0	Normal	MCI	2.0	1	27	45	No	0.54, 0.70	-
	Lacunar,	MCI mix	VaD							
	posterior,		MCI							
	NIHSS 1		mix							
	TIA, right side,		Normal							
	NIHSS 1		Normal							
	Cortical, left		Normal							
	side, NIHSS 0		Normal							
	Subcortical H,		Normal							
	left side,		MCI							
	NIHSS 1		AD							
	TIA left side,		Normal							
	NIHSS 0		MCI							
	Lacunar,		AD							
	posterior,									
	NIHSS 0									
	Lacunar, left									
	side, NIHSS 2									
	Cortical, left									
	side, NIHSS 1									
	TIA, left side,									
	NIHSS 0									

	Lacunar, right side, NIHSS 1 Lacunar, left side, NIHSS 0 Subcortical H, right side, NIHSS2 TIA, left side, NIHSS 0 Lacunar, right side, NIHSS 2 Cortical, left side, NIHHS 0				

ing; m=male; f=female; lacunar infarcts; subcortical small (<15 mm) infarcts in the distal distribution of deep penetrating vessels; cortical ffects regions of the cerebral cortex; TIA=Transient Ischemic Attack; NIHSS=National Institute of Health Stroke Scale; H=hemorrhage; cognitive impairment; mix=mixed disease; VaD= vascular disease; AD= neurodegenerative disease; MTA= medial temporal atrophy; al cortical atrophy; MSSE= Mini Mental State Examination ;TMT-A= trail making test A; (Aβ)-42= cerebrospinal fluid (CSF) amyloid-β

Figures

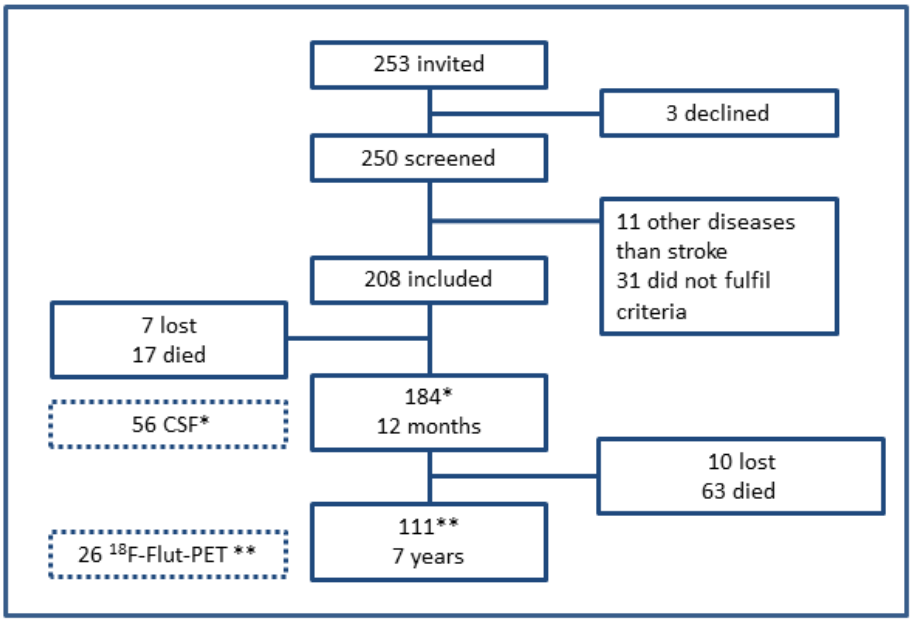

Figure 1

Flow chart

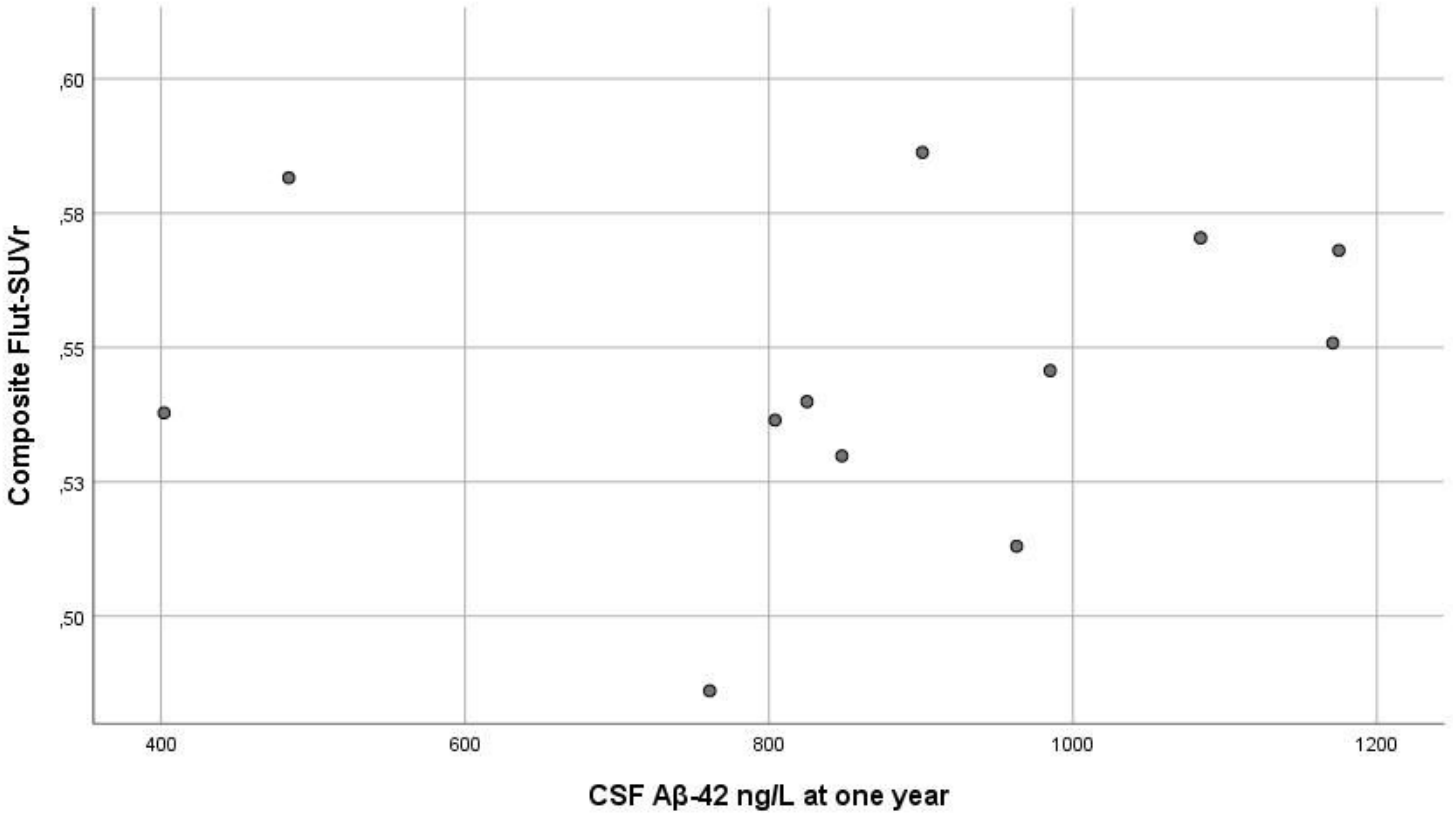

Figure 2

Associations between composite 18F-Flut-PET SUVr and CSF Aβ□□ levels at one year