Letter to the Editor

Prevalence of Amyloid Cerebral Deposits and Cognitive Outcome After Stroke: The IDEA3 Study

Olivier Godefroy,[1,2] Mélanie Barbay,[1,2] Jeanne Martin,[1,2] Trevor Shields,[3] Chantal Lamy,[1,2] Audrey Courselle-Arnoux,[1,2] Sandrine Canaple,[1,2] Claire Leclercq,[1,2] Martine Roussel,[1,2] Marc-Etienne Meyer,[3] Etienne Marchal,[3] Frank A. Wollenweber;[4] The IDEA3 Study Group

[1]Department of Neurology and [2]Laboratory of Functional Neurosciences (UR UPJV 4559), Amiens University Hospital, Amiens, France
[3]Department of Nuclear Imaging, Amiens University Hospital, Amiens, France
[4]Department of Neurology, Helios Dr. Horst Schmidt Kliniken, Wiesbaden and Institute for Stroke and Dementia Research, University Hospital of Munich (LMU), Munich, Germany

Dear Sir:

Some degree of cognitive impairment (CI) is observed in at least half of stroke survivors, two-thirds corresponding to mild CI and a third to dementia.[1] Regardless of severity, poststroke CI has severe consequences on autonomy, institutionalization,[2,3] quality of life,[4] and the rate of recurrence of a major vascular event and death.[5] Although poststroke CI is classically attributed to vascular brain lesions, pioneer studies reported that this accounts for only half of poststroke dementia.[6-8] A third of poststroke dementia has been attributed to associated Alzheimer's disease (AD) on clinical grounds.[6-8] With the development of amyloid positron emission tomography (PET), it is now possible to determine the presence of amyloid burden, a marker of AD, in poststroke CI. Four studies have assessed amyloid burden using PET following a stroke and reported a prevalence ranging from 10.5% to 22.2% in series of 26 to 81 patients.[9-12] Surprisingly only one study found a relationship with cognitive outcome at follow-up.[9] This wide range of prevalence and the questionable relationship with cognitive status raise serious questions concerning the previously reported contribution of AD to poststroke CI.

To address the contribution of amyloid burden to poststroke CI, we designed the IDEA3 (Imagerie des dépôts amyloïdes cérébraux par florbetapir [AV-45] et diagnostic des déficits cognitifs et démence post Accident Vasculaire Cérébral) study which assessed the amyloid PET status in stroke patients with some degree of CI and their outcome at 5 years. The main objective of the present study was to determine the frequency of amyloid PET positivity,

and the secondary objective was to determine the relationship with outcome at inclusion (i.e., at time of PET examination).

The inclusion criteria were similar to those of GRECogVASC (Groupe de Réflexion pour l'Évaluation Cognitive Vasculaire) study.[13] Briefly, eligible patients had to be hospitalized in our center for an acute (<30 days) ischemic or hemorrhagic stroke with positive imaging, to have at least one impaired cognitive score at the follow-up assessment, and to be free of exclusion criteria (Supplementary Method 1). The main exclusion criteria included known conditions (other than stroke) that affect cognition and large cerebellar lesions.

From September 2010 to February 2018, 91 patients were included in IDEA3 (Supplementary Figure 1). Infarcts were observed for 81 patients (89%); the 10 (11%) cerebral hemorrhages were mainly due to hypertension and cerebral amyloid angiopathy (Table 1). A group of 1,003 healthy volunteers were used to analyze the cognitive data.[14] The study was performed in accordance with institutional guidelines and was approved by the regional investigational review board (Comité de Protection de Personnes Nord-Ouest II, Amiens, France; reference: 2013/27, July 11, 2013) and informed consent was obtained from patients.

The screening visit was scheduled at 6 months poststroke and included clinical and cognitive assessments. Patients fitting the inclusion criteria and consenting to participate were then planned for the amyloid PET exam. The supply of florbetapir determined the date of the inclusion visit (M0), ideally scheduled in the first year after the stroke. However, severe supply delays led to later inclusion of the first patients. The inclusion visit corresponded

Table 1. Cohort characteristics and association according to PET status

	Total (n=91)	Amyloid		P
		Positive (n=14)	Negative (n=77)	
Acute phase				
Age (yr)	63.3±10.7	72.6±6.0	61.6±10.5	<0.001
Male sex	62 (68.1)	10 (71.4)	52 (67.5)	>0.99
Education (yr)	10.5±2.8	9.6±1.7	10.6±2.9	0.20
Prestroke IQCODE score	48.9±2.5	52.3±7.8	51.2±8.0	0.60
Prestroke modified Rankin Scale score	0 [0–0]	0 [0–0]	0 [0–1]	0.13
Prestroke 4IADL	0.3±1.1	0.86±2.4	0.16±0.5	0.40
NIHSS on admission	5.6±5.8	4.7±3.1	5.8±6.2	0.30
Acute complication	26 (37.7)	3 (30.0)	23 (39.0)	0.70
Delirium	2 (2.9)	0 (0.0)	2 (3.4)	>0.99
Cause of stroke				
Infarct subgroup (n=81)	81 (89.0)	12 (85.7)	69 (89.6)	0.60
Atherosclerosis	4 (4.9)	0 (0.0)	4 (5.8)	>0.99
Small vessel disease	14 (17.3)	4 (33.3)	10 (14.5)	0.20
Cardioembolic stroke	20 (24.7)	4 (33.3)	16 (23.2)	0.50
Other	8 (9.8)	1 (8.3)	7 (10.1)	0.80
Hemorrhage subgroup (n=10)	10 (11.0)	2 (14.3)	8 (10.4)	
Hypertensive	5 (50.0)	0 (0.0)	5 (62.5)	0.40
Amyloid angiopathy	3 (30.0)	2 (100)	1 (12.5)	0.06
Other	2 (20.0)	0 (0.0)	2 (25.0)	>0.99
Inclusion				
Time poststroke (days)	808±589	660±515	835±601	0.30
Recurrent stroke	1 (1.1)	0	1 (1.3)	>0.99
NIHSS	1.49±2.02	0.86±2.4	0.16±0.5	0.80
Depressive symptoms	14.5±11.3	15.7±11.1	14.3±11.3	0.70
MMSEa score	25.9±3.6	23.1±4.8	26.4±3.1	0.02
MoCA score	22.3±4.4	16.7±4.9	22.7±4.2	0.03
4IADL	1.76±2.31	2.0±3.16	1.71±2.14	0.70
Depressive symptoms	14.5±11.3	15.7±11.1	14.3±11.3	0.70
Behavioral dysexecutive score	1.76±2.31	2.0±3.16	1.71±2.14	0.70
4IADL	1.76±2.31	2.0±3.16	1.71±2.14	0.70
modified Rankin Scale score	2 [1–3]	2 [1–3]	2 [1–3]	0.90

Data are expressed as n (%), mean±standard deviation, or median [interquartile range].
PET, positron emission tomography; IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly; 4IADL, score on 4 Instrumental Activities of Daily Living; NIHSS, National Institutes of Health Stroke Scale; MMSEa, education-adjusted score on the Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment.

to the day of the PET examination and included clinical, neuropsychological, and magnetic resonance imaging (MRI) examination. This study focuses on data from the inclusion visit.

The clinical and cognitive assessments have been previously reported in the GRECogVASC study[13] and are detailed in the Supplementary Method 2. Cognitive scores were analyzed according to a validated framework[14] and provided age- and education-adjusted z scores for each domain (Supplementary Method 2).

The cognitive status (subjective cognitive complaint, mild CI, dementia) was defined using the VASCOG criteria (Vascular Behavioral and Cognitive Disorders).

18F-florbetapir PET was performed according to the recommended methods[15] (Supplementary Method 3). PET images were visually evaluated by trained nuclear medicine physicians blinded to the patient clinical information. Quantitative analyses were also performed and the corresponding standardized uptake value

ratios (SUVr) were calculated using the cerebellar cortex as a reference.[15] To avoid a confounding influence by the stroke lesion, the lesion was delineated on the corresponding MRI and excluded from the composite volume of interest (VOI) on the PET data. Patients with a global florbetapir SUVr ≥1.35 were considered to be amyloid positive. There was perfect agreement between the visual and quantitative interpretations (κ=1, P=0.0001). To examine whether stroke lesion could have promoted amyloid deposition, two additional analyses were performed. First, the SUVr of the peri-stroke region were determined using the Wollenweber methods (Supplementary Method 3) and compared to the homologous region in the contralateral hemisphere.[10] Second, we separately calculated the composite VOI of the ipsilesional and contralesional hemispheres. Their relationship was assessed using a correlation analysis between the composite VOIs of the ipsilesional and contralesional hemispheres.

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Florbetapir PET was positive for 14 patients (mean SUVr: 1.462± 0.091), corresponding to a prevalence of 15.4% (95% confidence interval: 7.97%–22.8%). The prevalence was similar (13.8%, 95% confidence interval: 6.5%–21%) in the 87 patients without pre-stroke CI (defined as Informant Questionnaire on Cognitive Decline in the Elderly score <55). PET imaging was delayed for a large proportion of patients due to late supplying of florbetapir, resulting in a mean poststroke time interval of approximately 2 years. This interval did not differ according to PET status (Table 1). The peri-stroke SUVr (1.56±0.3) was mildly lower (P=0.001) than that of the homologous VOI (1.62±0.3). The composite VOI of the ipsilesional hemisphere (1.20±0.17) was highly correlated (R=0.97, P= 0.0001) with that of the contralesional hemisphere (1.21±0.17).

Age- and education-adjusted scores on cognitive screening tests showed greater impairment among amyloid-positive patients (Table 1). Accordingly, analysis of variance showed cognitive z scores (Figure 1) to be lower (P=0.02) for amyloid-positive patients (z: -1.886±0.289, amyloid negative patients: -1.138±
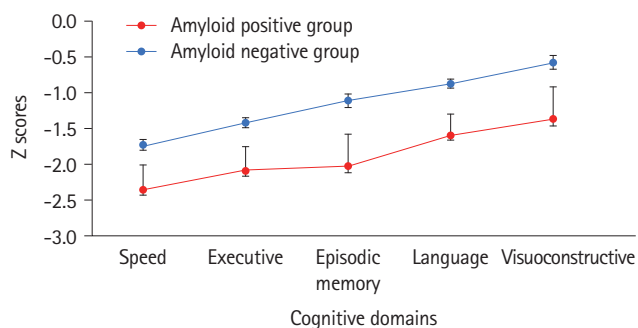
Figure 1. Z scores (standard error) of the five cognitive domains according to amyloid status.

0.123) and to differ according to domain (P=0.0001) due to better overall language and visuoconstructive scores, without interaction (P=0.9). The behavioral dysexecutive score did not differ (P=0.7) between groups (amyloid positive group: -1.857±2.8, amyloid negative group: -1.571±2.15).

Regarding cognitive status, logistic regression showed that dementia was more frequent (odds ratio: 6.44, 95% confidence interval: 1.14–36.6, P=0.04) in amyloid-positive (dementia: 28.6%; mild CI: 50%) than amyloid-negative patients (dementia: 7.78%; mild CI: 54.5%).

Finally, the stroke-PET time interval did not correlate with any significant findings: SUVr (R=-0.05, P=0.9), education-adjusted score on the Mini-Mental State Examination (R=0.1, P=0.3), and global cognitive score (R=-0.04, P=0.7).

The IDEA3 study shows cerebral amyloid positivity to be observed with a prevalence of 15.4% (95% confidence interval: 7.97%–22.8%) and associated with a more severe cognitive status. The present results were obtained with the largest population to date using comprehensive cognitive assessment. Together with previous reports,[9-12] they support a poststroke prevalence of amyloid positivity of approximately 15%–20%. Differences between studies are likely to be due to the inclusion of patients of different ages and varying cognitive status and this should be examined in a future study. Accordingly, we found both factors to be associated with amyloid status. The present study focused on patients with at least one abnormal cognitive score at one time point, as this typically raises the question of cognitive deficit and its cause in clinical practice.

The lack of association between stroke lesion and amyloid deposit supports previous reports.[10,16]

The present results demonstrate that the amyloid burden is associated with cognitive status. This supports the pioneering reports that suggested that a part of poststroke dementia is related to associated AD.[6-8] This association is independent of age (as all cognitive scores were adjusted for age and education) and poststroke time interval. The discrepancy with the three poststroke PET studies that did not find any relationship between amyloid burden and cognitive status can be explained by differing sample sizes.[10-12] Conversely, it is unlikely to be due to differences in the duration of follow-up, as negative results have been reported in long-term assessment.[11,12] We are currently assessing the effect of amyloid burden on long-term outcome, as the sole study showing a relationship with cognitive outcome documented greater cognitive decline over time.[9] The present study supports the lack of association between amyloid burden and behavioral disorders (including apathy) and depression.

Supplementary materials

Conflicts of interest

Olivier Godefroy reports no disclosures. Mélanie Barbay received funding for travel and meetings from Bristol Myers Squibb, Sanofi Aventis, Roche SAS, Biogen. Jeanne Martin reports no disclosures. Trevor Shields reports no disclosures. Chantal Lamy reports no disclosures. Audrey Courselle-Arnoux received funding for travel and meetings from Merk-Serono, Bristol Myers Squibb, Sanofi Aventis, Biogen, Teva-Santé, ISIS perfusion, Novartis. Sandrine Canaple reports no disclosures. Claire Leclercq received funding for travel and meetings from Sanofi Aventis, Biogen, Homeperf, Pfizer, Genzyme. Martine Roussel reports no disclosures. Marc-Etienne Meyer reports no disclosures. Etienne Marchal reports no disclosures. Frank A. Wollenweber received institutional study fees (DFG sponsored patients fees from the Find-AF2 Study), institutional (Alexion Pharm) and personal (Boehringer, Portola, Bayer und Pfizer BMS) speaker fees.

Author contribution

Conceptualization: OG. Study design: OG, MR. Methodology: OG, MR, MEM, FAW. Data collection: MB, CL, ACA, SC, CL, TS, EM, OG, MR. Investigation: TS, EM, JM. Statistical analysis: OG, FAW, TS, EM. Writing—original draft: OG, EM. Writing—review & editing: MB, CL, ACA, SC, CL, TS, EM, MEM, OG, MR, FAW. Funding acquisition: OG. Approval of final manuscript: all authors.

Acknowledgments

We thank Hassan Berrissoul and Astrid Causel for assistance with the organizational aspects of the study and collecting clinical data, as well as Quentin Legendre for help in collecting the MRI data.

References

1. Barbay M, Diouf M, Roussel M, Godefroy O; GRECOGVASC study group. Systematic review and meta-analysis of prevalence in post-stroke neurocognitive disorders in hospital-based studies. *Dement Geriatr Cogn Disord* 2018;46:322-334.
2. Tatemichi TK, Desmond DW, Stern Y, Paik M, Sano M, Bagiella E. Cognitive impairment after stroke: frequency, patterns, and relationship to functional abilities. *J Neurol Neurosurg Psychiatry* 1994;57:202-207.
3. Rockwood K, Wentzel C, Hachinski V, Hogan DB, MacKnight C, McDowell I. Prevalence and outcomes of vascular cognitive impairment. Vascular cognitive impairment investigators of the Canadian Study of Health and Aging. *Neurology* 2000;54: 447-451.
4. Haley WE, Roth DL, Kissela B, Perkins M, Howard G. Quality of life after stroke: a prospective longitudinal study. *Qual Life Res* 2011;20:799-806.
5. Desmond DW, Moroney JT, Bagiella E, Sano M, Stern Y. Dementia as a predictor of adverse outcomes following stroke: an evaluation of diagnostic methods. *Stroke* 1998;29:69-74.
6. Tatemichi TK, Desmond DW, Mayeux R, Paik M, Stern Y, Sano M, et al. Dementia after stroke: baseline frequency, risks, and clinical features in a hospitalized cohort. *Neurology* 1992;42: 1185-1193.
7. Kokmen E, Whisnant JP, O'Fallon WM, Chu CP, Beard CM. Dementia after ischemic stroke: a population-based study in Rochester, Minnesota (1960-1984). *Neurology* 1996;46:154-159.
8. Pohjasvaara T, Erkinjuntti T, Ylikoski R, Hietanen M, Vataja R, Kaste M. Clinical determinants of poststroke dementia. *Stroke* 1998;29:75-81.
9. Mok VCT, Lam BYK, Wang Z, Liu W, Au L, Leung EYL, et al. Delayed-onset dementia after stroke or transient ischemic attack. *Alzheimers Dement* 2016;12:1167-1176.
10. Wollenweber FA, Därr S, Müller C, Duering M, Buerger K, Zietemann V, et al. Prevalence of amyloid positron emission tomographic positivity in poststroke mild cognitive impairment. *Stroke* 2016;47:2645-2648.
11. Hagberg G, Ihle-Hansen H, Fure B, Thommessen B, Ihle-Hansen H, Øksengård AR, et al. No evidence for amyloid pathology as a key mediator of neurodegeneration post-stroke - a seven-year follow-up study. *BMC Neurol* 2020;20:174.
12. Koenig LN, McCue LM, Grant E, Massoumzadeh P, Roe CM, Xiong C, et al. Lack of association between acute stroke, poststroke dementia, race, and β-amyloid status. *Neuroimage Clin* 2021;29:102553.
13. Barbay M, Taillia H, Nédélec-Ciceri C, Bompaire F, Bonnin C, Varvat J, et al. Prevalence of poststroke neurocognitive disorders using National Institute of Neurological Disorders and Stroke-Canadian Stroke Network, VASCOG criteria (vascular behavioral and cognitive disorders), and optimized criteria of cognitive deficit. *Stroke* 2018;49:1141-1147.

14. Godefroy O, Gibbons L, Diouf M, Nyenhuis D, Roussel M, Black S, et al. Validation of an integrated method for determining cognitive ability: implications for routine assessments and clinical trials. *Cortex* 2014;54:51-62.

15. Wong DF, Rosenberg PB, Zhou Y, Kumar A, Raymont V, Ravert HT, et al. In vivo imaging of amyloid deposition in Alzheimer disease using the radioligand 18F-AV-45 (florbetapir F 18). *J Nucl Med* 2010;51:913-920.

16. 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* 2016;47:113-119.

Correspondence: Olivier Godefroy
Department of Neurology, Amiens University Hospital, 80054 Amiens, France
Tel: +33-322668240
E-mail: godefroy.olivier@chu-amiens.fr
https://orcid.org/0000-0001-6789-6620

Supplementary Methods

Method 1: Exclusion criteria

The main exclusion criteria were as follows: (1) known conditions (other than stroke) affecting cognition including neurological conditions (mental retardation, Alzheimer's disease or related condition, epilepsy, severe traumatic brain injury, Parkinson's disease, multiple sclerosis, a brain tumor, or brain radiotherapy), (2) previously diagnosed psychiatric conditions (schizophrenia and major psychiatric disorders requiring hospitalization for >2 days in a specialized setting), (3) general comorbidities (chronic alcoholism, substance addiction, liver, kidney, or respiratory failure, and paraneoplastic syndrome), (4) treatments affecting cognition (other than stable dosage levels of an anxiolytic or a serotoninergic antidepressant), (5) conditions precluding cognitive assessment (illiteracy, severe sensory or motor impairments, or alertness disorder—defined as a score ≥1 for item 1a of National Institutes of Health Stroke Scale [NIHSS]), (6) co-morbidities associated with a life expectancy <2 years, (7) contra-indication to magnetic resonance imaging (MRI), (8) large cerebellar lesions (as they precluded the determination of uptake value), (9) pregnancy, (10) legal guardianship, and (11) lack of written informed consent. The presence of aphasia, hemineglect, prior stroke, and abnormal Informant Questionnaire on Cognitive Decline in the Elderly (defined as score ≥55 for the 16 items version) were not exclusion criteria provided it was not due to a diagnosed disease other than stroke (such as Alzheimer's disease). As previously indicated,[13] patients unable to perform a cognitive test due to cognitive impairment (including aphasia) were considered impaired.

Method 2: Cognitive score combination

According to a previously validated procedure,[14] component scores were combined according to the cognitive domain: when several component z scores assessed the same domain, they were averaged to yield a domain score (action speed: Trail Making Test part B and digit symbol substitution test; cognitive executive functions: semantic fluency, "PVR" fluency, error on Trail Making Test part B minus error on Trail Making Test part A; episodic memory: third and delayed free recall of Free Cued Selective Reminding test; language: Shortened Boston Naming test; and visuoconstructive abilities: copy of the Rey–Osterrieth complex figure test). After checking the homo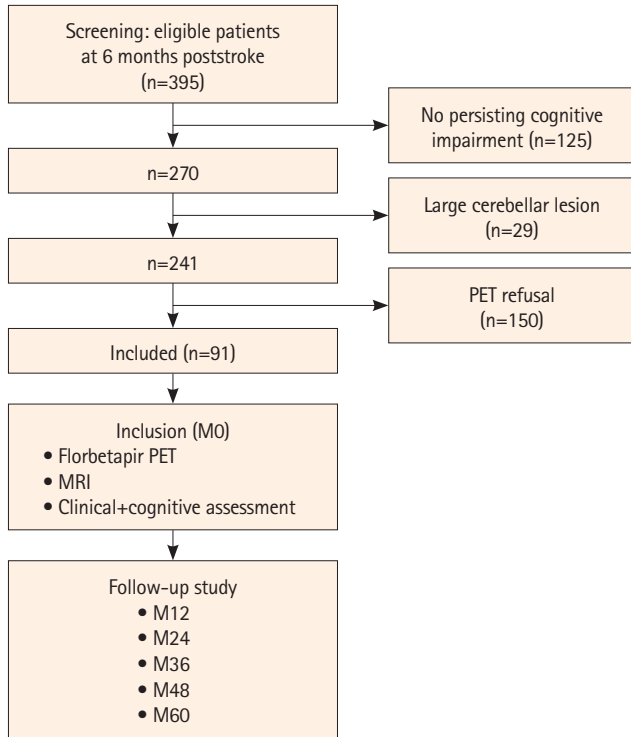geneity of the score distribution across the domains, the five domain scores were combined in the overall cognitive summary score, corresponding to the average of the five domain scores. Finally, the scores were categorized (i.e., normal or impaired) using the 5th percentile. Missing data were only interpreted as corresponding to an impairment when the neuropsychologist indicated that the patient was unable to perform the task.

Method 3: Amyloid positron emission tomography

Quantitative analyses were also performed according to the recommended methods.[15] Volumes of interest (VOIs) were applied to individual MR images and transferred to the co-registered positron emission tomography (PET) images using PMOD V3.407 (PMOD Technologies Ltd., Zurich, Switzerland). A composite VOI including frontal, parietal, lateral temporal and occipital cortex as well as the posterior cingulate was created, and the corresponding standardized uptake value ratios (SUVr) were calculated with the cerebellar cortex as a reference.[15] To avoid a confounding influence by the stroke lesion, the lesion mask (delineated on the corresponding MRI according to a previously validated method[15]) was excluded from the composite VOI on the PET data.

Patients with a global florbetapir SUVr ≥1.35 were considered to be amyloid positive. There was perfect agreement between the visual and quantitative interpretations ($\kappa=1$, $P=0.0001$).

To examine whether stroke lesion could have promoted amyloid deposition, two additional analyses were performed. First the SUVr of the peri-stroke region were determined in the 70 first patients (negative results led to the discontinuation of this analysis) and they were compared to those of the homologous region in the contralateral hemisphere using the methods of Wollenweber.[10] Briefly, the peri-stroke VOIs were drawn manually around the stroke lesion (using lesion mask delineated according to a previously validated method). The peristroke VOIs were then flipped on the y axis to determine the VOI in the homologous region of the contralateral hemisphere. SUVr was then calculated in both peri-stroke and homologous VOIs. They were compared using paired t-test. Second, we separately calculated the composite VOI of the ipsilesional and contralesional hemispheres. Their relationship was assessed using a correlation analysis between the composite VOIs of the ipsilesional and contralesional hemispheres.

Screening: eligible patients
at 6 months poststroke
(n=395)

No persisting cognitive
impairment (n=125)

n=270

Large cerebellar lesion
(n=29)

n=241

PET refusal
(n=150)

Included (n=91)

Inclusion (M0)
• Florbetapir PET
• MRI
• Clinical+cognitive assessment

Follow-up study
• M12
• M24
• M36
• M48
• M60

Supplementary Figure 1. Flow chart of the IDEA3 study. PET, positron emission tomography; MRI, magnetic resonance imaging; M, month.