PET imaging for the evaluation of cerebral amyloid angiopathy: a systematic review

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Abstract
Purpose In the last years, the role of PET imaging in the assessment of cerebral amyloid angiopathy (CAA) is emerging. In this setting, some tracers have proven their utility for the evaluation of the disease (mainly 11C-Pittsburgh compound B [11C-PIB]), however, the value of other radiotracers has to be clarified. The aim of this systematic review is, therefore, to assess the role of PET imaging in the evaluation of CAA.

Methods A wide literature search of the PubMed/MEDLINE, Scopus, Embase, Web of Science and Cochrane library databases was made to find relevant published articles about the diagnostic performance of PET imaging for the evaluation of CAA. Quality assessment including the risk of bias and applicability concerns was carried out using QUADAS-2 evaluation.

Results The comprehensive computer literature search revealed 651 articles. On reviewing the titles and abstracts, 622 articles were excluded because the reported data were not within the field of interest. Twenty-nine studies were included in the review. In general, PET imaging with amyloid tracers revealed its value for the assessment of CAA, for its differential diagnosis and a correlation with some clinico-pathological features. With less evidence, a role for 18F-fluorodeoxiglucose (18F-FDG) and tau tracers is starting to emerge.

Conclusion PET imaging demonstrated its utility for the assessment of CAA. In particular, amyloid tracers revealed higher retention in CAA patients, correlation with cerebral bleed, the ability to differentiate between CAA and other related conditions (such as Alzheimer's disease) and a correlation with some cerebrospinal fluid biomarkers.

Keywords PET · Positron emission tomography · Cerebral amyloid angiopathy · CAA · 11C-PIB · 11C-Pittsburgh compound B

Introduction
Cerebral amyloid angiopathy (CAA) is a neurological disorder caused by the deposition of β-amyloid in the walls of small and medium vessels of the cerebral cortex and leptomeninges [1, 2]. Its development is associated with multiple risk factors such as aging, the presence of Alzheimer’s disease (AD) and genetic mutations (apolipoprotein E [APOE] and amyloid-β protein precursor genes). In this setting, the prevalence of the disease is particularly evident in elderly patients [1, 3, 4].

The clinical manifestations of CAA can be really heterogeneous and can include a wide range of symptoms such as spontaneous lobar intracerebral hemorrhage (ICH), focal transient neurological episodes and cognitive impairment like dementia [1, 5–7]. In this scenario, ICH has central importance given its high recurrence rate estimated at more than 10% per year [1, 2].

Assessment of CAA is challenging and definitive diagnosis can be made only by postmortem histopathological confirmation by autopsy [1, 8]. In life, the disease is often recognized because of the presence of symptomatic and spontaneous ICH, preferentially affecting cortical-subcortical regions of occipital and posterior temporal lobes [2, 9]. In clinical practice, magnetic resonance (MR) imaging is mandatory for the correct evaluation of the patients, leading
material and methods

search strategy

A wide literature search of the PubMed/MEDLINE, Scopus, Embase, Cochrane Library and Web of Science databases was made to find significant published articles concerning the role of PET and PET/CT in the evaluation of CAA. Search algorithms were the following:

- "cerebral amyloid angiopathy" AND "PET"
- "cerebral amyloid angiopathy" AND "positron emission tomography"
- "cerebral amyloid angiopathy" AND "positron" AND "emission" AND "tomography"
- "cerebral" AND "amyloid" AND "angiopathy" AND "PET"
- "cerebral" AND "amyloid" AND "angiopathy" AND "positron emission tomography"
- "cerebral" AND "amyloid" AND "angiopathy" AND "positron" AND "emission" AND "tomography"
- "CAA" AND "PET"
- "CAA" AND "positron emission tomography"
- "CAA" AND "positron" AND "emission" AND "tomography".

No beginning date limit was applied to the search and it was updated until 31 January 2022. Only articles in the English language were considered. Furthermore, pre-clinical studies, postmortem studies, conference proceedings, reviews, case reports, case series and editorials were excluded from the review. To expand our search, the references of the retrieved articles were also screened for additional papers.

study selection

Two researchers (FD and DA) independently reviewed the titles and the abstracts of the retrieved articles. The full-text version of the remaining articles was then independently reviewed by the same authors, to determine their eligibility for inclusion. In addition to previously presented exclusion criteria, the presence of less than 8 patients affected by CAA was another criteria used to screen the articles, to avoid articles with small samples of patients. The quality assessment, including the risk of bias and applicability concerns was carried out using QUADAS-2 evaluation [16].

data abstraction

For each included study, data concerning the basic study were collected (first author, year of publication, country of origin, type of study) and PET device used, number of patients evaluated, and number of patients affected by CAA. The main findings of the articles included in this review are reported in the Results.

results

literature search

A total of 651 articles were extrapolated with the computer literature search and by reviewing the titles and abstracts, 622 of them were excluded because the reported data were not within the field of interest of this review. Twenty-nine articles were selected and retrieved in full-text version [17–45]; no additional studies were found screening the references of these articles (Fig. 1). Generally speaking, the quality assessment of these articles using QUADAS-2 underlined a low risk of bias (Fig. 2a) and low risks for applicability concerns (Fig. 2b).

Among the 29 studies included in the systematic review, 6 were of retrospective nature [22, 28, 29, 34, 39, 40] while 23 had a prospective design [17–21, 23–27, 30–33, 35–38, 41–45]. Regarding the device used for scan acquisition, 8 studies used PET only [17–24], 17 studies used PET/CT [25–32, 34–37, 39, 40, 42–45] while 3 studies used PET/MR [33, 38, 41]. Speaking about radiotracer, 11C-PIB was used in 13 studies [17–22, 28, 31, 32, 37, 41, 42, 45]. Speaking about radiotracer, 11C-PIB was used in 13 studies [17–22, 28, 31, 32, 37, 41, 42, 45].
one study [38]. Furthermore, some works used more than one tracer and in particular, a study used a combination of 
$^{18}$F-florbetapir and $^{11}$C-PIB [24], a study was performed with $^{11}$C-PIB and $^{18}$F-FBB [29], a study with $^{11}$C-PIB and $^{18}$F-T807 [43], a study with $^{11}$C-PIB and $^{18}$F-flortaucipir [44] and lastly a study used a combination of three different tracer ($^{11}$C-PIB, $^{18}$F-FBB and $^{18}$F-flutemetamol) [34]. The main characteristics of the studies and their results are briefly presented in Tables 1 and 2.

**Role of PET imaging for the assessment of CAA**

Many studies have proven the ability of $^{11}$C-PIB to concentrate in patients affected by CAA, demonstrating the usefulness of PET imaging for the assessment of the disease [17–22, 28, 31, 32, 37, 41, 42, 45]. Interestingly a single work revealed low specificity [21]. In this setting, a correlation between tracer uptake and the site of cerebral MB (CMB) was reported by some works [17, 19, 28, 40]. Furthermore, the role of PET imaging with $^{11}$C-PIB for the differential diagnosis between CAA and other conditions related to cerebral hemorrhage has been proven in some studies [18, 28, 32, 37, 42].

The ability of $^{11}$C-PIB PET imaging to differentiate between CAA and AD was investigated by some works [17, 18, 20, 22, 41] in general higher tracer retention was associated with the presence of CAA and occipital regions were characterized by higher uptake compared to AD.

PET imaging with $^{18}$F-florbetapir also revealed the ability to assess CAA [25, 30, 33, 35, 36]. In this setting, the correlation between tracer uptake and lobar ICH [25, 30] and with some cerebrospinal fluid (CSF) biomarkers were reported [33]. A single work revealed also a possible trend for $^{18}$F-florbetapir imaging to differentiate between AD and CAA-ICH [35]. Similarly, a new pharmacokinetic model has demonstrated the ability to differentiate probable CAA and deep ICH [38].

Three works investigated the role of $^{18}$F-FDG imaging in CAA [23, 39, 40], revealing its capability to differentiate between CAA-related and CAA-unrelated CMB [23] and between CAA and AD [40]. Furthermore, the value of $^{18}$F-FBB PET imaging was investigated by two works, demonstrating its ability to differentiate CAA-related inflammation (CAA-ri) from CAA and, with less evidences, from normal controls [26, 27].

Some works used mixed radiotracers for the assessment of CAA [24, 29, 34, 43, 44] and in this setting a correlation between $^{18}$F-florbetapir and $^{11}$C-PIB uptakes was demonstrated [24]. Furthermore, a similar proportion of positive scan between $^{18}$F-FBB and $^{11}$C-PIB was reported, with a correlation between some clinicopathological features and $^{18}$F-FBB positivity [29]. Both amyloid and tau deposition in CAA were evaluated by two different studies with the use of $^{11}$C-PIB and $^{18}$F-T807 [43] and $^{11}$C-PIB and $^{18}$F-flortaucipir [44], reporting that PET tau positivity was correlated with some clinicopathological features. Lastly, a single work used three tracer ($^{11}$C-PIB, $^{18}$F-FBB and $^{18}$F-flutemetamol) reporting a correlation between PET positivity and the pattern of MB presentation [34].

**Discussion**

**PET imaging with $^{11}$C-PIB**

As mentioned, several studies have investigated the role of PET imaging with $^{11}$C-PIB for the assessment of CAA [17–22, 28, 31, 32, 37, 41, 42, 45] demonstrating in general the capability of this tracer to be retained in patients affected by the disease.
Correlation with CMB and differential diagnosis of ICH

First, Dierksen et al. [17] demonstrated higher \(^{11}\text{C-PIB}\) retention in CAA compared to control subjects and a strong correlation between amyloid deposition and CMB, in particular for patients with high-CMB counts. Similarly, Gurol et al. [19] confirmed this correlation with new bleeds, reporting that increased tracer retention characterized sites of future bleeds and a higher risk of incidental bleeds. Again, Chang et al. [41] reported higher SUV values in CMB area of patients with CAA compared with those of AD or healthy subjects. In this setting Ly et al. [18] reported increased \(^{11}\text{C-PIB}\) uptake in patients with CAA-related hemorrhage (CAAH) and higher binding of tracer in patients with probable CAAH compared to patients with possible CAAH.
Four different studies by the group of Tsai et al. [28, 32, 37, 42] reported higher $^{11}$C-PIB retention in CAA-ICH patients compared to non-CAA-ICH patients (hypertensive and mixed ICH) and a correlation between lobar lacune counts and SUV values. Furthermore, higher tracer uptake in patients with high-degree enlarged centrum semiovale perivascular spaces (ECSPVS) compared to low-degree patients was reported.

Interestingly a study by Baron et al. [21] did not report differences in terms $^{11}$C-PIB uptake between CAA patients and healthy controls. In this work, $^{11}$C-PIB PET imaging revealed low specificity for CAA diagnosis, due to the frequent presence of high tracer uptake in the healthy elderly, reflecting incipient AD. However, a negative $^{11}$C-PIB was able to rule out CAA with excellent sensitivity.

Table 1 Characteristics of the studies considered for the review

| First author | References | Country | Year | Type of study | Isotope | N. Pts | Gender M:F | CAA pts |
|--------------|------------|---------|------|---------------|---------|--------|------------|--------|
| Dierksen     | [17]       | USA     | 2010 | Prospective   | $^{11}$C-PIB | 16     | 10:6       | 16 (100.0%) |
| Ly           | [18]       | Australia | 2010 | Prospective   | $^{11}$C-PIB | 42     | ns         | 20 (47.6%) |
| Gurol        | [19]       | USA     | 2012 | Prospective   | $^{11}$C-PIB | 11     | 9:2        | 11 (100.0%) |
| Gurol        | [20]       | USA     | 2013 | Prospective   | $^{11}$C-PIB | 135    | 78:57      | 42 (31.1%) |
| Baron        | [21]       | France, UK | 2014 | Prospective   | $^{11}$C-PIB | 31     | 24:7       | 11 (35.5%) |
| Farid        | [22]       | France, UK | 2015 | Retrospective | $^{11}$C-PIB | 31     | 24:7       | 11 (35.5%) |
| Samuraki     | [23]       | Japan   | 2015 | Prospective   | $^{18}$F-FDG | 158    | 70:88      | 17 (10.8%) |
| Gurol        | [24]       | USA     | 2016 | Prospective   | $^{18}$F-florbetapir, $^{11}$C-PIB | 19     | 13:6       | 10 (52.6%) |
| Raposo       | [25]       | France  | 2017 | Prospective   | $^{18}$F-florbetapir | 33     | 22:11      | 15 (45.5%) |
| Renard       | [26]       | France  | 2018 | Prospective   | $^{18}$F-florbetaben | 139    | 70:69      | 31 (22.3%) |
| Renard       | [27]       | France  | 2018 | Prospective   | $^{18}$F-florbetaben | 9      | 5:4        | 9 (100.0%) |
| Tsai         | [28]       | Taiwan, USA | 2018 | Retrospective | $^{11}$C-PIB | 110    | 68:42      | 24 (21.8%) |
| Jang         | [29]       | Korea, UK, USA | 2019 | Retrospective | $^{11}$C-PIB, $^{18}$F-florbetaben | 65     | 30:35      | 65 (100.0%) |
| Raposo       | [30]       | France  | 2019 | Prospective   | $^{18}$F-florbetapir | 38     | 23:15      | 18 (47.4%) |
| Schultz      | [31]       | USA, Netherlands, Australia | 2019 | Prospective   | $^{11}$C-PIB | 36     | 14:22      | 19 (52.8%) |
| Tsai         | [32]       | Taiwan, USA | 2019 | Prospective   | $^{11}$C-PIB | 80     | 53:27      | 13 (16.2%) |
| Banerjee     | [33]       | UK, Sweden | 2020 | Prospective   | $^{18}$F-florbetapir | 40     | 22:18      | 10 (25.0%) |
| Jung         | [34]       | Korea   | 2020 | Retrospective | $^{11}$C-PIB, $^{18}$F-florbetaben, $^{18}$F-flutemetamol | 71     | 31:40      | 71 (100%) |
| Planton      | [35]       | France  | 2020 | Prospective   | $^{18}$F-florbetapir | 35     | 21:14      | 15 (42.9%) |
| Planton      | [36]       | France  | 2020 | Prospective   | $^{18}$F-florbetapir | 36     | 22:14      | 18 (50.0%) |
| Tsai         | [37]       | Taiwan, France, USA | 2020 | Prospective   | $^{11}$C-PIB | 257    | 162:95     | 36 (14.0%) |
| Papanastasiou | [38]     | UK, Sweden | 2020 | Prospective   | $^{18}$F-flutemetamol | 16     | 10:6       | 8 (50.0%) |
| Bergeret     | [39]       | France  | 2021 | Retrospective | $^{18}$F-FDG | 35     | 17:18      | 14 (40.0%) |
| Bergeret     | [40]       | France  | 2021 | Retrospective | $^{18}$F-FDG | 14     | 8:6        | 14 (100.0%) |
| Chang        | [41]       | China   | 2021 | Prospective   | $^{11}$C-PIB | 39     | 27:12      | 9 (23.1%) |
| Tsai         | [42]       | Taiwan  | 2021 | Prospective   | $^{11}$C-PIB | 108    | 71:37      | 29 (26.8%) |
| Tsai         | [43]       | Taiwan  | 2021 | Prospective   | $^{11}$C-PIB, $^{18}$F-T807 | 76     | 53:23      | 20 (26.3%) |
| Schoemaker   | [44]       | USA, France | 2021 | Prospective   | $^{11}$C-PIB, $^{18}$F-flortaucipir | 46     | 32:14      | 46 (100.0%) |
| Gokcal       | [45]       | USA     | 2022 | Prospective   | $^{11}$C-PIB | 38     | 33:5       | 38 (100.0%) |

$N.$ number, $Pts$ patients, CAA cerebral amyloid angiopathy, $^{11}$C-PIB $^{11}$C-Pittsburgh compound B, $^{18}$F-FDG $^{18}$F-fluorodeoxyglucose

**Differential diagnosis between CAA and AD**

First Farid et al. [22] in a study with early and late phase imaging reported different $^{11}$C-PIB uptake for occipital and posterior cingulate cortex between AD and CAA, with lower whole cortex to occipital ratio and occipital/posterior cingulate ratio in CAA patients. Similarly, Dierksen et al. [17] reported an elevated occipital-to-global ratio for CAA patients compared to AD patients. In this scenario Chang et al. [41] reported lower global cortical $^{11}$C-PIB uptake for CAA patients compared to AD, however, tracer uptake in occipital regions was higher in CAA compared to AD patients. In contrast, AD subjects had higher lateral temporal lobe deposition of tracer. Similarly, Ly et al. [18] reported that $^{11}$C-PIB uptake in occipital-global neocortical and
| First author | References | Device | Activity | Uptake time | PET analysis | Main findings |
|-------------|------------|--------|----------|-------------|--------------|---------------|
| Dierksen    | [17]       | PET    | ns       | ns          | Qualitative and semiquantitative | Elevated tracer uptake in CAA and correlation with CMB. Higher occipital/global ratio compared to AD |
| Ly          | [18]       | PET    | 370 MBq  | Immediately | Qualitative and semiquantitative | Increased tracer uptake in CAA related hemorrhage |
| Gurol       | [19]       | PET    | 314.5–555 MBq | Immediately | Qualitative and semiquantitative | Correlation between tracer uptake and bleeds |
| Gurol       | [20]       | PET    | 314.5–555 MBq | Immediately | Qualitative and semiquantitative | Similar tracer retention between CAA and AD, correlation with WMH in CAA |
| Baron       | [21]       | PET    | 550 MBq  | Immediately | Qualitative and semiquantitative | PET imaging has low specificity for CAA |
| Farid       | [22]       | PET    | 550 MBq  | Immediately | Qualitative and semiquantitative | Tracer retention is different between CAA and AD |
| Samuraki    | [23]       | PET    | 370 MBq  | 40 min      | Qualitative and semiquantitative | Patients with CAA related CMB have a typical pattern of hypometabolism |
| Gurol       | [24]       | PET    | 370 MBq for $^{18}$F-florbetapir, 314.5–555 MBq for $^{11}$C-PIB | 50 min for $^{18}$F-florbetapir, immediately for $^{11}$C-PIB | Qualitative and semiquantitative | Strong correlation between the uptake of the tracers. Higher uptake for CAA compared to hypertensive ICH |
| Raposo      | [25]       | PET/CT | 3.7 MBq/Kg | 50 min      | Qualitative and semiquantitative | Higher tracer retention for CAA compared to deo ICH, in particular in occipital lobe |
| Renard      | [26]       | PET/CT | 300 MBq  | 90 min      | Qualitative and semiquantitative | Higher uptake in the pons for CAA-ri compared to CAA |
| Renard      | [27]       | PET/CT | 300 MBq  | 90 min      | Qualitative and semiquantitative | High tracer uptake for CAA-ri, in particular in occipital lobe |
| Tsai        | [28]       | PET/CT | 370 MBq  | 40 min      | Qualitative and semiquantitative | High tracer retention for CAA-ICH and correlation with lobar lacune counts |
| Jang        | [29]       | PET/CT | 420 MBq for $^{11}$C-PIB, 381 MBq for $^{18}$F-florbetaben | 60 min for $^{11}$C-PIB, 90 min for $^{18}$F-florbetaben | Qualitative and semiquantitative | Similar frequency of positive scans for the two tracers. Positive patients had worse cognitive tests. Higher occipital/global ratio for CAA compared to AD |
| Raposo      | [30]       | PET/CT | 3.7 MBq/Kg | 50 min      | Qualitative and semiquantitative | Higher tracer uptake for lobar ICH patients. Correlation between scan positivity and probability of CAA |
| Schultz     | [31]       | PET/CT | 314.5–555 MBq | Immediately | Qualitative and semiquantitative | High tracer uptake for APP E693Q mutation carriers |
| Tsai        | [32]       | PET/CT | 370 MBq  | 40 min      | Qualitative and semiquantitative | Higher tracer uptake for CAA-ICH patients compared to mixed ICH |
Table 2 (continued)

| First author | References | Device | Activity | Uptake time | PET analysis | Main findings |
|--------------|------------|--------|----------|-------------|--------------|---------------|
| Banerjee     | [33]       | PET/MR | 370 MBq  | Immediately | Qualitative and semiquantitative | Correlation between PET positivity and some CSF markers |
| Jung         | [34]       | PET/CT | 420 MBq for $^{11}$C-PIB, 381 MBq for $^{18}$F-florbetaben, 185 MBq for $^{18}$F-flutemetamol | 60 min for $^{11}$C-PIB, 90 min for $^{18}$F-florbetaben, 90 min for $^{18}$F-flutemetamol | Qualitative and semiquantitative | Frequency of positivity is correlated with pattern of MB |
| Planton      | [35]       | PET/CT | 3.7 MBq/Kg | 50 min | Qualitative and semiquantitative | Global tracer retention is higher in AD than in CAA, however, a trend for increased occipital/global ratio was present in CAA-ICH |
| Planton      | [36]       | PET/CT | 3.7 MBq/Kg | 50 min | Qualitative and semiquantitative | No different tracer uptake between ICH affected and non affected emisphere |
| Tsai         | [37]       | PET/CT | 314.5–555 MBq | 30–40 min | Qualitative and semiquantitative | High cerebral and cerebellar tracer retention for CAA-ICH patients |
| Papanastasiou | [38]     | PET/MR | 185 MBq  | Immediately | Qualitative and semiquantitative | PET/MR with a new pharmacokinetic model is able to differentiate CAA from deep ICH |
| Bergeret     | [39]       | PET/CT | 2.5 MBq/Kg | 30 min | Qualitative and semiquantitative | Lower occipital/posterior cingulate ratio in CAA compared to AD |
| Bergeret     | [40]       | PET/CT | 2.5 MBq/Kg | 30 min | Qualitative and semiquantitative | Strong glucose hypometabolism in posterior areas for CAA |
| Chang        | [41]       | PET/MR | 4.44–5.55 MBq/Kg | 40–60 min | Qualitative and semiquantitative | High tracer uptake for CAA but lower compared to AD. Nevertheless, higher uptake in occipital regions for CAA |
| Tsai         | [42]       | PET/CT | 370 MBq  | 40 min | Qualitative and semiquantitative | High amyloid burden for CAA-ICH and correlation between tracer uptake and ECSPVS |
| Tsai         | [43]       | PET/CT | 370 MBq for $^{11}$C-PIB, 370 MBq for $^{18}$F-T807 | 40 min | Qualitative and semiquantitative | Low $^{11}$C-PIB uptake for SVD compared to CAA. Correlation between $^{18}$F-T807 uptake and TREM2. A certain quote of CAA has tau PET positivity |
| Schoemaker   | [44]       | PET/CT | 314.5–370 mCi for $^{11}$C-PIB, 333–407 mCi for $^{18}$F-flortaucipir | Immediately for $^{11}$C-PIB, 80–100 min for $^{18}$F-flortaucipir | Qualitative and semiquantitative | Correlation between $^{18}$F-flortaucipir uptake in amnestic forms of CAA and memory performances |
| Gokcal       | [45]       | PET/CT | 314.5–555 MBq | 60 min | Qualitative and semiquantitative | Tracer uptake is correlated with vascular reactivity in mediating WMH |

PET positron emission tomography, PET/CT positron emission tomography/computed tomography, PET/MR positron emission tomography/magnetic resonance, CAA cerebral amyloid angiopathy, CMB cerebral microbleeds, AD Alzheimer’s disease, MBq megabecquerel, WMH white matter hyperintensities, ICH intracerebral hemorrhage, APP amyloid precursor protein, CSF cerebrospinal fluid, ECSPVS enlarged centrum semiovale perivascular spaces, SVD small vessels disease, $^{11}$C-PIB $^{11}$C-Pittsburgh compound B, TREM2 triggering receptor expressed on myeloid cell2
frontal-global neocortical regions was somewhat different between CAAH and AD patients.

Interestingly Gurol et al. [20] reported similar high 11C-PIB retention between CAA and AD patients, but a correlation between tracer uptake and white matter hyperintensities (WMH) in CAA patients.

Miscellany

Gokcal et al. [45] reported that 11C-PIB uptake was correlated with vascular reactivity, consistent with their hypothesis of the mediating role of this reactivity between tracer uptake and WMH.

Lastly, a singular work on patients with hereditary autosomal dominant forms of CAA was proposed by Schultz et al. [31], reporting high 11C-PIB uptake in these patients and an inverse correlation between uptake and Aβ40 levels in CSF.

PET imaging with 18F-florbetapir

Correlation between PET imaging and ICH

First, the group by Raposo et al. [25, 26] reported greater cortical 18F-florbetapir retention for CAA patients than deep ICH patients and a higher ratio of positive PET scan for lobar ICH than deep ICH. Furthermore, among CAA patients the highest uptake was present in the occipital lobe and a value of 1.18 for global SUVR (standardized uptake value ratio with cerebellum as reference) was obtained. Interestingly, in patients with lobar ICH the ratio of positive scan decreased in concordance with the probability of CAA diagnosis and PET positivity was independently correlated with ECSPVS.

More recently Planton et al. [36] investigated whether amyloid burden was increased in the ICH-affected emisphere in patients with asymptomatic CAA-ICH, reporting no differences between the two emispheres.

Miscellany

In their analysis of CSF biomarkers in CAA, Banerjee et al. [33] reported that half of CAA patients had a positive 18F-florbetapir PET scan. Furthermore, these patients had lower Aβ42, higher t-tau, higher p-tau, NFL and neogranin. compared to patients with negative PET scans were demonstrated.

Planton et al. [35] reported higher global retention of 18F-florbetapir in mild cognitive impairment (MCI)-AD patients compared to CAA subjects, however, no differences were reported for relative regional uptake. Nevertheless, a trend for increased occipital/global ratio in CAA-ICH patients was reported.

PET imaging with 18F-FDG

First, Samuraki et al. [23] investigated the role of 18F-FDG for the assessment of CAA in patients with probable AD, reporting that patients with CAA-related CMB had hypometabolism mainly in left temporal lobe and in bilateral insular gyri. Conversely, patients with CAA-unrelated CMBs had reduced tracer uptake mainly in the right putamen and right cerebellum. Furthermore, a positive correlation between Mini-Mental State Examination (MMSE) and verbal memory score with 18F-FDG uptake were recognized.

More recently two different works by the group Bergeret et al. [39, 40] investigated the possible role of 18F-FDG PET imaging to differentiate CAA from AD. Lower occipital/posterior cingulate SUVR ratio in CAA patients compared to AD subjects was demonstrated. Furthermore, with the exception of the anterior cingulate and medial prefrontal cortex, patients with CAA had global cortical significant glucose hypometabolism, however, significant only in the posterior areas.

PET imaging with 18F-FBB and 18F-flutemetamol

The role of 18F-FBB in CAA was evaluated in two studies by the group Renard et al. [26, 27]. They reported general higher tracer uptake for CAA-ri patients compared to normal control, in particular in the occipital lobe with a posterior to anterior trend, however, without significant difference between the lobes. Furthermore, higher SUVR of the pons in CAA-ri patients compared to CAA subjects was reported. When considering pons as the reference standard, a correlation between Aβ40 and SUVR was underlined.

More recently, Papanastasiou et al. [38] demonstrated the role of a new pharmacokinetic model with PET/MR able to separately detect impaired haemodynamic and amiloyd load in patients with probable CAA compared to patients with deep ICH. These findings were also reproducible with a reduced time acquisition and underlined an overlapping in perfusion deficits and amyloid burden in patients with CAA-related ICH.

PET imaging with mixed radiotracers

First, the role of 18F-florbetapir and 11C-PIB in the assessment of CAA was evaluated by Gurol et al. [24], demonstrating a strong correlation between the uptake of the two tracers. Furthermore, mean global cortical 18F-florbetapir uptake and mean occipital SUVR were higher for CAA patients compared to patients with deep hypertensive ICH.

Jang et al. [29] used both 18F-FBB and 11C-PIB to evaluate patients with probable CAA with a positive scan percentage of 66.7% for 11C-PIB and 66% for 18F-FBB. Interestingly, patients with positive amyloid PET (Aβ+)
had a higher frequency of APOE ε4 carriers, more CMB, a higher frequency of cortical superficial siderosis and worse performances in cognitive tests. Furthermore, occipital global SUVR was higher for Aβ + CAA patients in comparison to Aβ + AD patients.

An evaluation of patients with cerebral small vessels disease (SVD), including also CAA subjects, was made by Tsai et al. [43] with ¹¹C-PIB and ¹⁸F-T807 to assess both amyloid and tau cortical deposition. They reported that 33.3% of CAA patients had a positive ¹⁸F-T807 scan and patients with a positive tau scan (both AD and CAA) had higher triggering receptor expressed on myeloid cell 2 (TREM2) plasma levels; furthermore, these levels correlated with MMSE score. Both amyloid and tau evaluation was also performed by Schoemaker et al. [44]. General high global retention of ¹¹C-PIB and increased ¹⁸F-flortaucipir retention for amnestic CAA patients compared to non-amnestic forms were reported. Furthermore, patients with positive ¹⁸F-flortaucipir PET scans had lower performances in the memory domain.

Lastly, Jung et al. [34] used three tracers (¹¹C-PIB, ¹⁸F-FBB and ¹⁸F-flutemetamol) to evaluate patients with CAA, revealing that the frequency of PET positivity was correlated with the pattern of MB presentation.

In conclusion, generally speaking PET imaging demonstrated its utility for the assessment of CAA. In particular, β-amiloid tracers revealed higher retention in CAA patients, correlation with CMB, the ability to differentiate between CAA and other related conditions (such as AD) and a correlation with some CSF biomarkers. The role of ¹⁸F-FDG imaging for the differential diagnosis of CAA and its correlation with cognitive performances are arising, however, with initial evidence. Similarly, the use of tau PET imaging in CAA is starting to emerge.

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Declarations
Conflict of interest All The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Given the retrospective nature of the study, no specific ethical approval was required.

Inform consent Informed consent was obtained from all individual participants included in the study.

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