Featured Article

Cerebral amyloid angiopathy in Down syndrome and sporadic and autosomal-dominant Alzheimer’s disease

María Carmona-Iragui, Mircea Balasa, Daniel Alcolea, Susana Fernández, Laura Videla, Isabel Sala, María Belén Sánchez-Saudinos, Estrella Morenas-Rodriguez, Roser Ribosa-Nogue, Ignacio Illán-Gala, Sofía Gonzalez-Ortiz, Jordi Clarimón, Frederick Schmitt, David K. Powell, Beatriz Bosch, Albert Llado, Michael Rafii, Elizabeth Head, José Luis Molinuevo, Rafael Blesa, Sebastián Videla, Alberto Lleo, Raquel Sánchez-Valle, Juan Fortea

Abstract

Introduction: We aimed to investigate if cerebral amyloid angiopathy (CAA) is more frequent in genetically determined than in sporadic early-onset forms of Alzheimer’s disease (AD) (early-onset AD [EOAD]).

Methods: Neuroimaging features of CAA, apolipoprotein (APOE), and cerebrospinal fluid amyloid-β (Aβ) 40 levels were studied in subjects with Down syndrome (DS, n = 117), autosomal-dominant AD (ADAD, n = 29), sporadic EOAD (n = 42), and healthy controls (n = 68).

Results: CAA was present in 31%, 38%, and 12% of cognitively impaired DS, symptomatic ADAD, and sporadic EOAD subjects and in 13% and 4% of cognitively unimpaired DS individuals and healthy controls, respectively. APOE ε4 genotype was borderline significantly associated with CAA in sporadic EOAD (P = .06) but not with DS or ADAD. There were no differences in Aβ40 levels between groups or between subjects with and without CAA.

Discussion: CAA is more frequently found in genetically determined AD than in sporadic EOAD. Cerebrospinal fluid Aβ40 levels are not a useful biomarker for CAA in AD.

Keywords: Cerebral amyloid angiopathy; Sporadic early-onset Alzheimer’s disease; Autosomal-dominant Alzheimer’s disease; Down syndrome; Neuroimaging; Cerebrospinal fluid biomarkers

1 These authors contributed equally to the manuscript.
2 These authors share senior authorship.
3 Corresponding author. Tel.: +34 935565986; Fax: +34 935565602.
4 E-mail address: jfortea@santpau.cat

© 2017 Published by Elsevier Inc. on behalf of the Alzheimer’s Association.

http://dx.doi.org/10.1016/j.jalz.2017.03.007
1552-5260/© 2017 Published by Elsevier Inc. on behalf of the Alzheimer’s Association.
1. Introduction

Most cases of Alzheimer’s disease (AD) are sporadic and caused by complex interactions between genetic and environmental factors. In approximately 5% of cases, AD can present clinically before the age of 65 years (early-onset AD [EOAD]) [1]. These patients frequently present with nonamnestic phenotypes and faster clinical decline than older sporadic AD cases [1]. In 0.1% to 0.5% of cases, AD is transmitted with an autosomal-dominant pattern of inheritance (autosomal-dominant AD [ADAD]) due to the presence of mutations in presenilin 1 (PSEN1), presenilin 2 (PSEN2), or amyloid precursor protein (APP) genes [2]. Down syndrome (DS) is also recognized as a form of genetically determined AD, mainly caused by the APP gene triplication [2]. Despite the different genetic background, the AD neuropathologic findings in sporadic EOAD, ADAD, and DS are very similar [3,4].

Cerebral amyloid angiopathy (CAA) is a major cause of lobar intracerebral hemorrhage (ICH) in the elderly and is present in up to 90% of AD brains at autopsy [3]. Previous neuropathologic studies have suggested a more severe CAA in ADAD than in sporadic AD [4]. CAA in some APP mutations or duplication carriers drives the clinical presentation [4] and is also consistently observed in subjects with DS [5]. The modified Boston criteria for CAA (mBCAA)–related hemorrhage have been validated to attribute in vivo an ICH to CAA based on several neuroimaging features and are frequently used in clinical practice [6]. There are no previous studies systematically assessing the CAA neuroimaging features in DS and ADAD.

Amyloid β (Aβ)40 is the major form of Aβ deposited in the vessel walls in individuals with CAA. Low levels of Aβ40 and Aβ42 have been found in the cerebrospinal fluid (CSF) of subjects with sporadic CAA [7]. However, scarce and contradictory data are available about the CAA CSF biomarker profile in sporadic AD patients [8–10], and no previous studies have assessed this profile in DS or ADAD. Moreover, the apolipoprotein (APOE) ε4 genotype is a risk factor for both sporadic AD and sporadic CAA [11], as it increases Aβ deposition in both the parenchyma and blood vessels [12]. However, the effect of the APOE genotype in AD dementia within DS and ADAD is controversial, and there are no studies assessing the influence of the APOE genotype on CAA in ADAD or DS [13].

The differences in the CAA neuroimaging features and CSF biomarkers profile in the different forms of AD are, thus, not established. Our primary objective was to determine the CAA presence by assessing the fulfillment of the mBCAA and the CSF Aβ40 levels in three different AD populations (DS, ADAD, and EOAD). We hypothesized that patients with genetically determined AD would have more CAA neuroimaging and biochemical features than EOAD.

2. Materials and methods

2.1. Study design and participants

A total of 256 subjects were recruited from five centers: Hospital de Sant Pau, Hospital Clinic de Barcelona, and Barcelona Down Medical Center in Barcelona, Spain; and the Sanders-Brown Center on Aging in Kentucky, and the Down Syndrome Biomarker Initiative project in San Diego, USA. Four study groups were evaluated: EOAD, ADAD, DS, and healthy controls (HCs).

EOAD (N = 42): patients were recruited at the Memory Unit of Hospital de Sant Pau from the Sant Pau Initiative on Neurodegeneration (Barcelona SPIN cohort) [14]. We used the International Working Group-2 for AD with in vivo evidence of AD based on CSF biomarkers [2]. This group included 19 individuals with prodromal EOAD (pEOAD) and 23 subjects with probable dementia in EOAD (dEOAD).

ADAD (N = 29): participants were recruited from the Genetic Counseling Program for familial dementias (PICOGEN) at the Hospital Clinic de Barcelona [15]. Fifteen symptomatic carriers (CDR ≥ 0.5) carrying nine different PSEN1 mutations (M139T, S169P, L173F, G209E, L235R, K239N, L282R, L286P, and I439S) and one symptomatic carrier of the APP I716T mutation were included. The symptomatic carriers were further classified as prodromal AD in ADAD (pAD-ADAD, n = 5) and dementia in ADAD (dAD-ADAD, n = 11). Twelve presymptomatic mutation carriers (CDR = 0) carrying seven different PSEN1 mutations (M139T, S169P, L173F, R220G, K239N, L282R, and I439S) and one presymptomatic carrier of APP mutation (I716T) were labeled as asymptomatic ADAD. We used the International Working Group-2 diagnostic criteria for AD [2].

DS (N = 117): adults with DS were recruited from three centers—the Down Alzheimer Barcelona Neuroimaging Initiative in the Barcelona Down Medical Center [16]; the Sanders-Brown Center on Aging; and the Down Syndrome Biomarker Initiative pilot project [17]. Adapted neuropsychological batteries (detailed in the Appendix section) covering all cognitive domains classified DS participants into “without cognitive decline” (asymptomatic DS, n = 91), prodromal AD in DS (pAD-DS, n = 13), and AD dementia in DS (dAD-DS, n = 13). Participants with pAD-DS and dAD-DS were also labeled as symptomatic DS participants.

HCs (N = 68): participants were recruited at Hospital de Sant Pau (n = 60) and Hospital Clinic de Barcelona (n = 8) enrolled among patients’ caregivers. They did not have cognitive complaints, scored zero on CDR, had normal neuropsychological evaluation, and normal core AD CSF biomarkers [18,19].

2.2. Procedures

Medical records were reviewed for potential confounders; and effect modifiers, age, sex, and presence of
The radiological evaluation was performed by two raters (either M.C.-I or M.B.; neurologists with expertise in cognitive disorders and S.G.; neuroradiologist) blinded to the clinical data. Inter-rater reliability was above 90% and discrepancies within ratings were solved by consensus.

2.4. CSF biomarkers and APOE genotype

The inclusion criteria included CSF data for EOAD and HCs but not for ADAD and DS. Details of analysis are described elsewhere [14,18]. In short, commercially available ELISA kits were used to determine CSF Aβ40 and Aβ42 levels (Millipore and Fujirebio-Europe, respectively), following the manufacturers’ recommendations.

APOE genotyping was performed by PCR amplification of the exon 4 fragment containing the two polymorphisms (rs429358 and rs7412) that encode the three common APOE isoforms. The following oligonucleotides, APOE-F: 5'-ACTGGAAGAACACTGACC-3' and APOE-R: 5'-CTGGCCATCTCTCCATC-3', were used and final PCR products were purified and Sanger sequenced using BigDye Terminator Chemistry (Applied Biosystems). Sequences were run on an Applied Biosystems 3130 Genetic Analyzer, and resulting electropherograms were visually inspected using Sequencer (version 4.1; Gene Codes Corporation).

2.5. Statistical analysis

Statistical analyses were performed with the Statistical Package for the Social Sciences, v19 software (IBM Corp. http://www-01.ibm.com/software/es/analytics/spss/). The primary objectives of this study were to compare across arterial hypertension, and neuropsychological information on disease severity (Mini–Mental State Examination [MMSE] for EOAD and ADAD and the Cambridge Examination for mental Disorders of Older People with DS and Others with Intellectual Disabilities—A Cognitive Scale for DS) were recorded and sent to the coordinating center (Hospital de Sant Pau) with the CSF biomarkers (Aβ42 and Aβ40) and neuroimaging data.

The study was approved by the local Ethics Committees following the ethical standards recommended by the Declaration of Helsinki. All participants and/or their caregivers gave their written informed consent.

2.3. Neuroimaging assessments

The inclusion criteria for all participants included a 1.5T or 3T magnetic resonance imaging (MRI) scan including T2* gradient echo (GRE) or susceptibility weighted imaging (SWI), axial fluid attenuated inversion recovery, and coronal T1-weighted sequences in the five centers involved. GRE or SWI sequences were assessed for the presence of the main CAA neuroimaging features: localization and number of lobar microbleeds, presence of cortical superficial siderosis (cSS), and lobar ICH. We evaluated the fulfillment of mBCAA in all participants regardless of the age criterion included in the criteria set (>55 years) [6]. White matter hyperintensities (WMHs) were semiquantitatively assessed in fluid attenuated inversion recovery sequences according to the Fazekas score [20]. Medial temporal atrophy (MTA) was evaluated in coronal T1-weighted images through the Scheltens scale [21]. MTA was scored bilaterally and the highest score was considered for the analyses.

Table 1

Demographics and CSF biomarker characteristics of the participants

<table>
<thead>
<tr>
<th></th>
<th>Healthy controls</th>
<th>Sporadic EOAD</th>
<th>Asymptomatic ADAD</th>
<th>Symptomatic ADAD</th>
<th>Asymptomatic DS</th>
<th>Symptomatic DS</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>68</td>
<td>19</td>
<td>23</td>
<td>13</td>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td>Age, y</td>
<td>54.3 (9)</td>
<td>60.9 (8)</td>
<td>61.8 (7)</td>
<td>53.6 (11)</td>
<td>54.8 (17)</td>
<td>47.3 (10)</td>
</tr>
<tr>
<td>Gender, % men</td>
<td>35.3</td>
<td>26.3</td>
<td>39.1</td>
<td>23.1</td>
<td>33.6</td>
<td>60</td>
</tr>
<tr>
<td>High blood pressure</td>
<td>13.2</td>
<td>21.1</td>
<td>13</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>APOE ε4 carriers, %</td>
<td>32.4</td>
<td>73.3</td>
<td>43.5</td>
<td>7.7</td>
<td>0</td>
<td>18.2</td>
</tr>
<tr>
<td>APOE ε2 carriers, %</td>
<td>4.4</td>
<td>5.3</td>
<td>4.3</td>
<td>7.7</td>
<td>0</td>
<td>27.3</td>
</tr>
<tr>
<td>MMSE/total CAMCOG</td>
<td>29 (2)</td>
<td>28 (2)</td>
<td>20 (7)</td>
<td>30 (1)</td>
<td>24 (4)</td>
<td>20 (7)</td>
</tr>
</tbody>
</table>

Abbreviations: Aβ40, amyloid-b40; Aβ42, amyloid-b4-2; APOE, apolipoprotein E; CAMCOG-DS, Cambridge Examination for Mental Disorders of Older People with Down Syndrome and Others with Intellectual Disabilities—Cognitive Scale; CSF, cerebrospinal fluid; DADAD, dementia in autosomal-dominant Alzheimer’s disease; dAD-DS, Alzheimer’s disease dementia in Down syndrome; d-EOAD, dementia in early-onset Alzheimer’s disease; EOAD, early-onset Alzheimer’s disease; MMSE, Mini–Mental State Examination; pAD-ADAD, prodromal Alzheimer’s disease in autosomal-dominant Alzheimer’s disease; pAD-DS, prodromal Alzheimer’s disease in Down syndrome; p-EOAD, prodromal sporadic early-onset Alzheimer’s disease.

NOTE. Unless otherwise specified, values are presented as medians (interquartile range). CSF was available from 66/68 HCs, 19/19 p-EOAD, 23/23 d-EOAD, 7/13 asymptomatic ADAD, 5/5 pAD-ADAD, 9/11 dAD-ADAD, 36/91 asymptomatic DS, 9/13 pAD-DS, and 6/13 dAD-DS.

*Median relative age (interquartile range) was 11.9 (14.4), 3.15 (6.5), and 3.5 (4.8) in asymptomatic ADAD, pAD-ADAD, and dAD-DS, respectively.

APOE was available from 66/68 HCs, 19/19 p-EOAD, 23/23 d-EOAD, 13/13 asymptomatic ADAD, 5/5 pAD-ADAD, 117/DS, 78/91 asymptomatic DS, 10/13 pAD-DS, and 12/13 dAD-DS.

CAMCOG score was available in 55/91 asymptomatic DS subjects, 7/14 pAD-DS subjects, and 3/12 dAD-DS subjects.
groups the frequency of the mBCAA and the CSF Aβ40 levels and were analyzed with the Fisher’s exact and Mann-Whitney tests, respectively.

The secondary tests were to assess the white matter lesions measured by the Fazekas scale and the hippocampal atrophy measured by the Scheltens scale and were analyzed with the Fisher’s exact test. Spearman correlation coefficients were calculated between age, clinical stage, hippocampal atrophy and white matter lesions, and the different study groups. With the purpose of improving the statistical power, prodromal and demented groups in EOAD, ADAD, and DS were merged when analyzed. All significance tests were two sided with the statistical significance set at 5%.

3. Results

Table 1 displays the demographics, clinical features, CSF data, and APOE genotype of the participants. CSF data were available in 71% (N = 182) of the subjects (including all HCs and patients with EOAD). Symptomatic ADAD and symptomatic DS subjects were younger than patients with EOAD (48.4, 54.4, and 61.1 years of age, respectively; P < .001).

The APOE ε4 allele frequency was higher in EOAD than in any other group. However, no differences were observed between symptomatic or asymptomatic subjects within the ADAD or DS groups.

Table 2 shows the neuroimaging results across the different groups. The fulfillment of the mBCAA was more frequent in symptomatic DS (31%, N = 8) and symptomatic ADAD (38%, N = 6), than in EOAD (24%, N = 19; P = .055 and P = .026, respectively). When present, the most frequent CAA neuroimaging features were lobar microbleeds in 91.2% (N = 31), followed by cSS in 29.4% (N = 10) and ICH in 8.8% (N = 3). All three features were more frequent in the symptomatic than in asymptomatic subjects within all groups (Table 2).

The symptomatic ADAD and DS groups had a higher proportion of lobar microbleeds than the EOAD group (P = .02 and P = .046, respectively). cSS and ICH were statistically associated (P = .004). In those who had cSS, 20% (N = 2) also had an ICH, and cSS was present in 67% (N = 2) of those with ICH. Symptomatic DS had a higher proportion of subjects with cSS and lobar ICH than the EOAD group, but this difference did not reach statistical significance (P = .056). The position of the mutation (precodon 200 or postcodon 200) did not significantly impact the presence of lobar microbleeds in PSEN1 carriers (37% vs. 25%, P = .4). One of the asymptomatic ADAD participants included in our study had a massive lobar ICH after recruitment into this study that led to the participant’s death in a stage of moderately severe dementia.

The mean time lag between MRI and CSF sampling was 5.3 months. Symptomatic participants had lower CSF Aβ40 levels than asymptomatic subjects within all groups (Fig. 1A). No significant differences were detected in CSF Aβ40 levels between the different groups or between symptomatic and asymptomatic subjects within each group (Fig. 1B).

### Table 2: Neuroimaging findings

<table>
<thead>
<tr>
<th></th>
<th>Healthy controls</th>
<th>Sporadic EOAD</th>
<th>Asymptomatic ADAD</th>
<th>Symptomatic ADAD</th>
<th>Asymptomatic DS</th>
<th>Symptomatic DS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>p-EOAD</td>
<td>d-EOAD</td>
<td></td>
<td>pAD-ADAD</td>
<td>dADAD</td>
</tr>
<tr>
<td>N</td>
<td>68</td>
<td>19</td>
<td>23</td>
<td>13</td>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td>MRI (GRE/SWI), %</td>
<td>38.2/61.8</td>
<td>24.1/57.9</td>
<td>39.1/60.9</td>
<td>100/0</td>
<td>100/0</td>
<td>46.2/53.8</td>
</tr>
<tr>
<td>Lobar microbleeds, %</td>
<td>2.9</td>
<td>10.5</td>
<td>8.7</td>
<td>0</td>
<td>20</td>
<td>45.5</td>
</tr>
<tr>
<td>cSS, %</td>
<td>1.5</td>
<td>0</td>
<td>8.7</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lobar ICH</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Boston criteria</td>
<td>4.4</td>
<td>10.5</td>
<td>13</td>
<td>0</td>
<td>20</td>
<td>45.5</td>
</tr>
<tr>
<td>Fazekas</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Score 0</td>
<td>64.7</td>
<td>21.1</td>
<td>26.1</td>
<td>75</td>
<td>40</td>
<td>27.3</td>
</tr>
<tr>
<td>Score 1</td>
<td>32.4</td>
<td>52.6</td>
<td>65.2</td>
<td>25</td>
<td>40</td>
<td>72.7</td>
</tr>
<tr>
<td>Score 2</td>
<td>2.9</td>
<td>15.8</td>
<td>8.7</td>
<td>0</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>Score 3</td>
<td>0</td>
<td>10.5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>MTA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Score 0–1</td>
<td>97.1</td>
<td>52.6</td>
<td>56.5</td>
<td>100</td>
<td>100</td>
<td>63.6</td>
</tr>
<tr>
<td>Score 2–4</td>
<td>2.9</td>
<td>47.4</td>
<td>43.5</td>
<td>0</td>
<td>0</td>
<td>36.4</td>
</tr>
</tbody>
</table>

Abbreviations: Aβ40, amyloid-β40; Aβ42, amyloid-β 1–42; APOE, apolipoprotein E; CAMCOG-DS, Cambridge Cognition Examination for mental disorders of older people with Down syndrome and others with intellectual disabilities; CSF, cerebrospinal fluid; cSS, cortical superficial siderosis; dADAD, dementia in autosomal-dominant Alzheimer’s disease; dAD-DS, Alzheimer’s disease dementia in Down syndrome; d-EOAD, dementia in sporadic early-onset Alzheimer’s disease; EOAD, early-onset Alzheimer’s disease; GRE, gradient echo sequences; ICH, intracerebral hemorrhage; MMSE, Mini–Mental State Examination; MRI, magnetic resonance imaging; MTA, medial temporal atrophy; pAD-ADAD, prodromal Alzheimer’s disease in autosomal-dominant Alzheimer’s disease; pAD-DS, prodromal Alzheimer’s disease in Down syndrome; p-EOAD, prodromal early-onset Alzheimer’s disease; SWI, susceptibility weighted imaging.

NOTE. Unless otherwise specified, values are presented as proportions.

*Fazekas score was not available in four asymptomatic DS subjects and in two dAD-DS subjects.

MTA score was not available in one AD subject, in three asymptomatic DS subjects, one pAD-DS subject, and one dAD-DS subject.
All EOAD patients fulfilling the mBCAA were APOE ε4 carriers, and the APOE ε4 allele was significantly more frequent in EOAD subjects than in the symptomatic ADAD (P = .015) or symptomatic DS (P = .071) participants fulfilling the mBCAA. In sporadic EOAD, there was a trend for the association between mBCAA fulfillment and APOE ε4 genotype (P = .06).

There were no differences in CSF Aβ42 levels between those subjects who fulfilled the mBCAA and those who did not (or the presence of lobar microbleeds, cSS, or ICH) in any group.

Symptomatic subjects presented higher Fazekas scores than asymptomatic subjects in all groups: EOAD patients had higher Fazekas scores than HCs (P < .001); symptomatic ADAD higher than asymptomatic ADAD (P = .022) or HCs (P = .05); and symptomatic DS higher than asymptomatic DS (P = .011) and HCs (P < .001; Fig. 2 and Table 2).

There was a significant positive correlation between age and Fazekas score in the whole sample (r = .337, P < .001), in ADAD (r = .407, P = .031), and in DS (r = .506, P = .000) groups. This correlation was also found in asymptomatic DS (r = .495, P < .001) and in HCs (r = .323, P = .007; Fig. 3).

Age positively correlated with Scheltens scores in the whole sample (r = .229, P < .001), HCs (r = .276, P = .023), ADAD (r = .412, P = .027), asymptomatic DS (r = .341, P = .001), and symptomatic DS (r = .431, P = .023). The Scheltens scores increased from asymptomatic to symptomatic subjects within each group. Symptomatic DS patients presented higher MTA scores than EOAD and symptomatic ADAD patients (P < .001 in each comparison) and asymptomatic DS subjects higher than HCs (P < .001). There were no differences in Scheltens scores between EOAD and symptomatic ADAD.

4. Discussion

We found that DS and ADAD have a more severe CAA than EOAD as measured by the mBCAA, but CAA did not impact the CSF Aβ42 levels. The APOE ε4 allele might be associated with CAA in EOAD but does not seem to have an effect in DS or ADAD.

There are previous studies assessing the prevalence of lobar microbleeds in ADAD and EOAD [22–24], but, to our knowledge, none has specifically assessed and compared the mBCAA between the different AD populations. The mBCAA were more frequent in DS and ADAD, suggesting a more severe CAA, as shown in pathologic studies [5,25]. The most frequent CAA neuroimaging feature was the presence of lobar microbleeds, as previously described [26]. The frequency of lobar microbleeds in ADAD (and HCs) was in agreement with the literature (ranging from 25% to 66%) [23,24,26], but we found a lower frequency of lobar microbleeds in ADAD (and HCs) than those subjects who fulfilled the mBCAA for possible or probable CAA. No differences in levels of CSF Aβ40 or Aβ42 were detected between subjects that fulfilled mBCAA and those who did not within each clinical group. Abbreviations: AD, Alzheimer’s disease; ADAD, autosomal-dominant Alzheimer’s disease; CAA, cerebral amyloid angiopathy; CSF, cerebrospinal fluid; DS, Down syndrome; EOAD, early-onset Alzheimer’s disease.
There are no previous studies assessing the mBCAA or any of its component neuroimaging features in DS. CAA is also consistently observed in DS pathologic studies [5, 28], but it had been proposed that other genetic factors in DS might protect these subjects from the ICH [29]. We found 38.5% of frequency for lobar microbleeds in symptomatic DS and, more importantly, a frequency of 15.4% for ICH. Although this is lower than the reported 30% prevalence for symptomatic ICH in non–trisomic APP duplication carriers, it is well above the 3% to 3.8% figure for symptomatic ICH in DS reported in the same study [29]. This discrepancy might be explained because many nonfatal ICHs might be unnoticed in DS with AD. Of note, both subjects with DS and ICH on the MRI did not present with ICH-related clinical symptoms.

A significant percentage of symptomatic subjects, nonetheless, did not meet the mBCAA and were free of the CAA-associated neuroimaging features. This is in contrast with pathologic studies, where CAA is found in up to 90% of AD brains, suggesting that the available MRI sequences only identify a subset of AD-CAA subjects [23]. The CAA neuroimaging features might, thus, detect only the most severe cases or, alternatively, they might select different subgroups of patients [23]. In this respect, cSS, although less frequent than lobar microbleeds, was strongly associated with lobar ICH. cSS might be a particularly important marker for severe CAA in AD, as it has been suggested in sporadic CAA [7]. More work in longitudinal studies is needed to confirm the higher risk conferred by cSS for future ICH and cognitive decline.

We also assessed other neuroimaging features associated with CAA but not included in the mBCAA. Both WMHs and MTA are increasingly recognized as core AD features and as a manifestation of CAA [30]. We found a gradient in WMH extension in all groups [31], but we also found more extended WMHs in those subjects fulfilling the mBCAA. WMHs also increased with age and in relation with vascular risk factors. We found this correlation also in HCs, although...
they all had normal core AD CSF biomarkers and low prevalence of high blood pressure. However, we found a strong correlation between age and WMHs in asymptomatic DS despite their younger mean age. This correlation supports the relationship between amyloid deposition and WMHs. Not surprisingly, the Scheltens scores increased with symptom severity in all AD populations. Hippocampal atrophy, however, was more severe in DS, even in asymptomatic DS individuals. These results are in agreement with the notion that individuals with DS not only have smaller hippocampal size from birth but also show atrophy when AD develops [17].

Decreased CSF Aβ40 levels might differentiate sporadic CAA from HCs and AD cases [7]. In our study, nevertheless, CSF Aβ40 levels did not discriminate CAA neuroimaging features in any group. This finding could be influenced by the fact that amyloid vascular burden in CAA in ADAD and DS contains not just Aβ40, but also Aβ42. It is difficult to sort out the contribution of vascular Aβ42 deposition from parenchymal plaque deposition except with neuropathologic

Fig. 3. Proportion of subjects according to Fazekas score by the range of age. The frequency bar graphs showing the percentage of subjects with each Fazekas categories by age: (A) healthy controls and (B) asymptomatic Down syndrome subjects.
analysis of the postmortem brain, which was not available in this study [32,33].

To our knowledge, there are only two studies that determine CSF Aβ40 in participants with AD with and without lobar microbleeds and show conflicting findings [9,10]. In any case, our results suggest that CSF Aβ40 levels are not a sensitive biomarker to detect CAA in the context of an AD process.

The APOE ε4 allele confers a higher risk for CAA in the general population and in AD [11,12]. We also found a trend for an association between APOE ε4 genotype and CAA in sporadic EOAD. Furthermore, all EOAD subjects with CAA neuroimaging features were APOE ε4 carriers. We did not find this relationship in ADAD or DS. The APOE ε4 genotype might be thus associated with CAA in EOAD but not in DS or ADAD. In ADAD and DS, other genetic factors, such as the type or position of the causing mutation in ADAD, might be more important in predicting CAA [4].

Our findings have potential clinical implications. The mBCAA have not been validated in patients <55 years of age. We consider that, at least in ADAD and DS, age should not be an essential requirement for CAA diagnosis. Our results also have substantial implications in AD clinical trials given the relationship between CAA and amyloid-related neuroimaging abnormalities (ARIAs). Vascular amyloid may be a pathophysiological mechanism for ARIAs [34,35], and recent studies have shown that after Aβ immunotherapy, there is an increase in CAA severity and an increase in lobar microbleeds associated with removal of plaques [36]. Trials targeting Aβ commonly use lobar microbleeds and APOE genotype to stratify subjects [37]. However, there are no available data on the relationship of CAA neuroimaging abnormalities (and APOE) and ARIAs in the setting of amyloid-lowering therapy in ADAD and DS. Our data emphasize heterogeneity in prevalence and possibly etiology for CAA; therefore, the recommendations on the exclusions for presence of baseline ARIA-H (microbleeds or hemosiderosis) from sporadic AD should be taken with caution. On the other hand, the APOE ε4 genotype is also commonly used to stratify participants given its influence on ARIAs [37]; however, this strategy might not be as important in ADAD or DS. Finally, our data also suggest that the CSF Aβ40 levels will not be a useful biomarker in these trials.

The higher prevalence of CAA in ADAD and DS might play a role in the conversion to clinical dementia. In sporadic AD, CAA is an independent contributor to cognitive impairment and can worsen the severity of cognitive dysfunction [38]. Future longitudinal studies are needed to assess the CAA contribution to cognitive impairment in ADAD and DS.

The main strengths of the present study are the relatively large sample size of different rare populations, such as ADAD and DS and the confirmation of the clinical diagnosis with genetics or CSF biomarkers. The study has some limitations. The use of two different imaging techniques is an important limitation when estimating the real prevalence of lobar microbleeds. SWI has a higher sensitivity for hemosiderin, detecting up to 50% more lobar microbleeds than conventional T2*GRE [39]. However, in our study, the ADAD group was exclusively investigated using T2*GRE, leading to a possible underestimation of the CAA neuroimaging features in these subjects. Finally, most of the EOAD patients were at a stage of mild dementia, and we lack neuropathologic data.

In conclusion, the CAA-associated neuroimaging features are more frequent in adults with DS and in patients with ADAD than in those with EOAD suggesting a more severe CAA pathology. Our study also shows that the CSF Aβ40 levels are not a reliable biomarker for CAA and that the risk factors for CAA (such as the APOE ε4 genotype) might be different in EOAD and genetically determined AD. These findings should be taken into account in the design of clinical trials with antiamyloid therapies in people with ADAD or DS.

Acknowledgments

The authors thank the participants and their families for their generosity. We want to acknowledge Laia Muñoz and Raúl Núñez for the laboratory and sample handling.

This work has been partially supported by research grants from the Carlos III National Institute of Health of Spain (PI11/01532 to R.B.; PI14/01126 to J.F.; PI14/00036 and PI12/00013 to R.S.V.) jointly funded by Fondo Europeo de Desarrollo Regional, Unión Europea, “Una manera de hacer Europa”; Fundación Marató TV3 (project 20141210 to J.F.); and CIBERNED (Program 1, Alzheimer Disease and Other Dementias to A.L.). This work has also been partially supported by a grant from the Gifolds Foundation, the Generalitat de Catalunya (2014SGR-0235), and by the Fundación Catalana de Síndrome de Down. Funding to support imaging studies in Down syndrome studies from UKY to E.H./F.S./D.K.P. is from NIH NICHD (R01HD064993). M.C-I. is supported by Contra no Marató TV3 and Raúl Núñez and for the laboratory and sample handling.

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jalz.2017.03.007.
**RESEARCH IN CONTEXT**

- To our knowledge, cerebral amyloid angiopathy (CAA) neuroimaging features have not been systematically assessed in subjects with sporadic early-onset Alzheimer’s disease (AD), autosomal-dominant AD, or Down syndrome. Only the frequency of lobar microbleeds in autosomal-dominant AD (25%–66%) has been reported. Regarding the CAA characterization from a cerebrospinal fluid (CSF) biomarker profile or APOE genotype point of view, there are no published data in these three populations of AD.

- This is the first study that includes a systematic assessment of the modified Boston criteria for CAA and other related features in sporadic early-onset AD, autosomal-dominant AD, and Down syndrome. This is also the first study that determines CSF amyloid-β Aβ40 or Aβ42 levels and APOE genotype in those populations of AD within the study of CAA. Our results show that CAA is more frequent in genetically determined cases of AD than in sporadic early-onset AD; however, these differences are not reflected in CSF Aβ40 or Aβ42 levels.

**References**


**FLA 5.4.0 DTD**  ■  JALZ2382_proof  ■  29 April 2017  ■  5:53 pm  ■  cc


