Characteristics of patients with amyloid-beta-related Cerebral Amyloid Angiopathy presenting in a dementia clinic

George P. Paraskevas¹, Vasilios C. Constantinides¹, Anastasia Bougea¹, Panagiotis Paraskevas², Georgios Tsivgoulis³, Elisabeth Kapaki¹*

¹1st Department of Neurology, Cognitive and Movement Disorders Clinic and Neurochemistry and Biological Markers Unit, School of Medicine, National and Kapodistrian University of Athens, Eginition Hospital, Athens, Greece
²Technological Educational Institute of Crete, School of Health and Welfare Services, Nursing Department, Heraklion, Crete, Greece
³2nd Department of Neurology, Medical School, National and Kapodistrian University of Athens, Attikon Hospital, Athens, Greece

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*Corresponding author: Elisabeth Kapaki, MD, PhD, Professor of Neurology and Neurochemistry, 1st Department of Neurology, Cognitive and Movement Disorders Clinic and Unit of Neurochemistry and Biological Markers, School of Medicine, National and Kapodistrian University of Athens, Eginition Hospital, 74 Vas. Sophias Ave., Athens 11528, Greece. Tel: ++302107289294; Fax: ++302107216474; E-mail address: ekapaki@med.uoa.gr

Abstract

Background: An important cause of cerebral amyloid angiopathy (CAA) is amyloid beta (Aβ) deposition and intracranial hemorrhage is a typical presentation. However, cognitive impairment is also a frequent finding and, some patients may present with dementia without a clinically evident previous hemorrhagic event.

Aim: The aim of the present study was to analyze the clinical, imaging and cerebrospinal fluid (CSF) characteristics of patients with Aβ-related CAA seeking attention in a tertiary academic center specialized in cognitive disorders.

Methods: We studied the clinical, imaging and CSF characteristics of all consecutive patients with cognitive complaints, examined during a 3-year period and having imaging (but not necessarily clinical) evidence of CAA and low Aβ42 in the CSF.

Results: Six patients fulfilled the inclusion criteria. Practically, all were compatible with the CSF biomarker profile of Alzheimer’s disease (AD). Only one patient suffered of clinically evident lobar hemorrhage. Seizure-like and ischemic-like symptoms were present in 50% and 17% respectively. Cognitive disorder was the presenting symptom in half, and the remaining half developed cognitive symptoms during the disease progress. Pyramidal or parkinsonian signs were present in 67%. Only 1 patient had the hippocampal amnestic type of dementia, typically expected in AD. All others had mixed or atypical profiles with frontal-sub cortical, visuospatial, language and psychiatric-behavioral components and, 2 patients would otherwise receive the clinical diagnosis of frontotemporal dementia or dementia with Lewy bodies.

Conclusion: Patients with Aβ-related CAA presenting in cognitive disorder departments seem to have a low percentage of clinically evident hemorrhagic events and a high percentage of dementia with an atypical, non-amnestic profile.

Keywords: Cerebral amyloid angiopathy, Amyloid beta, total tau, phospho-tau, cerebrospinal fluid, Alzheimer’s disease.

Introduction

Cerebral amyloid angiopathy (CAA) is characterized by amyloid deposition mainly in leptomeningeal and cortical vessels of medium size or less (especially small arteries, arterioles and capillaries), due to many causes, according to the amyloid protein involved [1]. An important cause is amyloid beta (Aβ) deposition which may occur: (a) alone sporadically (especially in the elderly), (b) related to sporadic Alzheimer’s disease (AD) or (c) in hereditary forms of AD or CAA including families with mutations in the genes of Amyloid Precursor Protein and presenilins 1 or 2 [2]. In AD, 82%–98% of patients show pathological evidence of some degree of CAA which may be severe in 30% [3–5]. In such disorders, both Aβ with 42 amino acid residues (Aβ42) and, especially, with 40 amino acid residues (Aβ40) accumulate in the vessel wall, while Aβ42 is the major component of parenchymal deposits (amyloid plaques) in AD [3]. The resulting vessel wall pathology leads to either hemorrhagic complications including lobar hemorrhage, cortical/cortiosubcorticalmicrobleeds, cortical superficial siderosis (cSS) and focal/convexal subarachnoid hemorrhage (SH), or ischemic complications including white matter (micro) ischemic lesions or cortical...
infarcts [1]. A subset of patients may develop an inflammatory response, either CAA-related inflammation or Aβ-related angiitis [6].

A clinically evident intracranial hemorrhage of lobar or corticossubcortical location is a typical presentation and, for such patients, diagnosis is based on the modified Boston criteria [7]. However, cognitive impairment due to AD, vascular pathology or both is also a frequent finding[8] and some patients may present with dementia without a clinically evident previous hemorrhagic event. The aim of the present study was to investigate the clinical, imaging and cerebrospinal fluid (CSF) characteristics of patients with Aβ-related CAA seeking attention, not in a stroke department, but in a tertiary academic center specialized in cognitive disorders.

Methods

Patients

We studied, all consecutive patients seeking attention for cognitive complaints in our department for a 3-year period (From January 2015 to December 2017) and having evidence of Aβ-related CAA Inclusion criteria included:

a) Magnetic resonance imaging (MRI) demonstrating multiple (micro) hemorrhages of lobar, cortical or corticossubcortical location, or at least one such (micro) hemorrhage with additional focal or disseminated cSS (based on the modified Boston criteria [7].

b) Disease onset at ≥55 years of age,

c) CSF biomarker evidence of amyloid pathology (low Aβ42).

d) Absence of severe uncontrolled hypertension (well controlled, mild-moderate hypertension was allowed).

e) Absence of other causes of hemorrhage (trauma, anticoagulants, blood dyscrasia or coagulopathy, vascular malformations).

f) Absence of abnormal findings in magnetic resonance angiography and neck vessel ultrasonography and

g) Absence of comorbidities including abnormal thyroid, B12, TPHA/VDRL, liver and renal function tests.

After history-taking and clinical examination, all patients had a complete neuropsychological examination including global cognitive tests and tests for memory, frontal-executive, language and visuoconstructive functions, and activities of daily living, depression and psychiatric/behavioral symptoms. Based on clinical, neuropsychological, MRI, and CSF biomarker findings, the cognitive disorder was diagnosed according to widely accepted criteria for AD [9–11], Dementia with Lewy Bodies (DLB) [12] or frontotemporal dementia of the behavioral type (bvFTD) [13].

All subjects and/or relatives gave informed consent for inclusion in the study. The study was in accordance with the ethical guidelines of the 1964 Declaration of Helsinki and had the approval of the Scientific and Ethics Committee of Egnition Hospital.

CSF sampling and biomarker determination

Lumbar puncture was performed at 10–11 am, after overnight fasting, at the L4-L5 interspace, according to recently proposed recommendations on standardized operating procedures (SOPs) for CSF biomarkers [14], as described elsewhere [15]. In brief, 4 polypropylene tubes were used for CSF collection. The initial tube (2 ml) was used for routine cytology and biochemistry. The next tube (2 ml) was used for IgG index and oligoclonal bands determination and syphilis serology. The last 2 tubes (5 ml each) were immediately centrifuged, aliquoted in polypropylene tubes (750 µl each) and, finally, stored at –80°C until analysis. Aliquots were thawed only once, just before analysis, which was performed within the 1st year of storage in all subjects.

The CSF levels of total tau protein (τT), amyloid-β peptide (1–42) (Aβ42) and tau phosphorylated at threonine-181 (τp-181) were measured in duplicate and blind to clinical diagnosis by double sandwich, enzyme-linked immunosorbent assay (ELISA) as provided by commercially available kits (“Innotest Tau antigen”, “β-amyloid1-42” and “phospho-tau181” respectively, Fujirebio, Gent, Belgium) according to manufacturer’s instructions. All determinations were performed by the use of a 4-parameter logistic curve. In-house standards were used during every run in order to ensure minimal measurement error (≤3.3%) and inter-assay and intra-assay variations ≤6.6% for all 3 biomarker assays [16]. Abnormal results were based on current cut-off values of our laboratory (τT ≥ 376, Aβ42 ≤ 580 and τP-181 ≥ 62.5 pg/ml) [15].

Neuromaging

All patients underwent brain MRI studies with the classical T1, T2, fluid attenuated inversion recovery (FLAIR) and T1 with gadolinium sequences. Additionally, T2* or susceptibility-weighted imaging (SWI) sequences were obtained in all patients.

Results

A total of 6 patients (3 females, 3 males) fulfilled the inclusion criteria and were included in the study (Table 1). Mean (SD) age at disease onset was 74.5 (8.2) years. Four patients (67%) had senile onset (>65 years of age) and the remaining 2 (33%) had an age of onset at 64–65 years. All but one (83%) had at least one classical cardiovascular risk factor and 3 (50%) had at least another 1st degree relative with dementia (with or without additional history of stroke), although specific details about the type of dementia and stroke were not available.

a) Clinical features

One patient (17%) presented with lobar hemorrhage (#1), while in another two (#5,6) imaging evidence of previous such hemorrhages was evident (33%, total 50%).Seizures were the presenting feature in one patient (#2, 17%) and developed later on in another two (#5 and 6, 33%, total 50%). One patient (#5) presented with transient ischemic attacks (TIA}s) and ishemic strokes (17%).Three patients (#3,4,6, 50%) presented with cognitive symptoms, progressing to dementia. All patients with non-cognitive presentation developed cognitive impairment later.
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### Table 1: Demographic, clinical, imaging and biochemical data of the studied patients

<table>
<thead>
<tr>
<th>#Sex</th>
<th>Age (y)</th>
<th>Risk factors and family history</th>
<th>Presenting symptom(s)</th>
<th>Accompanying or later symptom(s)</th>
<th>CSF</th>
<th>Imaging</th>
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<tbody>
<tr>
<td>1F</td>
<td>64</td>
<td>Hypertension</td>
<td>At age 64 left frontal lobar hemorrhage</td>
<td>Frontal MCI and significant anxiety-depression</td>
<td>τT↑, τP-181↑, Aβ42↓</td>
<td>WMLs, lobar hemorrhage, microbleeds</td>
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<tr>
<td>2F</td>
<td>78</td>
<td>Hypertension</td>
<td>Generalized seizures starting at age 75, responding well to oxcarbazepine</td>
<td>At age 76 MCI. Now, mild non-amnestic dementia with frontal and especially visuoconstructive components.</td>
<td>τT↑, τP-181↑, Aβ42↓</td>
<td>WMLs, mild hippocampal atrophy, microbleeds</td>
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Father and sister with dementia at age 77 and 75 respectively

| 3M   | 69      | None reported                    | At age 65 irritability, mild atypical language disorder | At age 67 non-amnestic dementia with significant executive and behavioral disorder (FTD-like) and anomic language difficulty with mixed logopenic and semantic features. Mild pyramidal signs with no gait difficulty | τT↑, τP-181↑, Aβ42↓ CSF protein↑ | WMLs, microbleeds, mild hippocampal atrophy |
| 4F   | 71      | Hypertension, diabetes type II.   | At age 70 atypical depression, followed by misidentification syndrome, visual hallucinations and sensitivity to haloperidol | Now severe frontal/visuospatial dementia with delusions, hallucinations, fluctuations and symmetric non-tremor parkinsonism with gait difficulty (DLB-like) | τT↑, τP-181↑, Aβ42↓ | WMLs, microbleeds |
| 5M   | 78      | Hypertension, dyslipidemia        | At age 72-77 TIAs, mild ischemic strokes | At age 75 simple partial seizures responding to lamotrigine. | Aβ42↓ Normal τT and τP-181↓ CSF protein↑ | WMLs, infarcts, cSS, microbleeds, remnants of corticosubcortical hemorrhage, hippocampal atrophy |
| 6M   | 87      | Hypertension, dyslipidemia, diabetes type II. Father and brother with senile-onset dementia | At age 72 amnestic MCI, gradually dementia (mainly amnestic, AD-like) | At age 87 complex partial seizures, responding well to levetiracetam. | τT↑, τP-181↑, Aβ42↓ protein↑ | WMLs, infarct, cSS, at least one corticosubcortical (micro) hemorrhage, hippocampal atrophy |

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Dementia was of the amnestic type (AD-like) in only 1 patient (#6, 17%) and received the diagnosis of possible AD with etiologically mixed (concomitant cerebrovascular) presentation and evidence (high) of AD pathophysiological process according to the NIA-AA criteria [9], or mixed AD with cerebrovascular disease according to IWG-2 criteria [11]. Another patient (#5, 17%) had a mixed neuropsychological profile and could receive the diagnosis of possible AD with etiologically mixed (concomitant cerebrovascular) presentation, according to the NIA-AA criteria, but evidence for AD pathophysiological process was intermediate [9]. One patient (#4, 17%) fulfilled the clinical criteria for DLB according to the 4th consensus report of the DLB consortium [12] and would also receive the diagnosis of possible AD dementia with evidence of AD, pathophysiological process according to the NIA-AA criteria [9]. Another patient (#3, 17%) would otherwise fulfill the International consensus criteria for probable bvFTD [13], except for the strong biomarker evidence for the presence of AD process, which reduces the diagnostic certainty to possible behavioral FTD and makes him fulfill the IWG-2 criteria for mixed AD (frontal variant with cerebrovascular disease) [11]. Two additional patients (#1, 2, 33%) had mainly frontal and/or visuoconstructive/visuospatial syndromes and fulfilled the IWG-2 criteria of mixed AD (atypical with cerebrovascular disease) [11].

b) CSF findings

Median values (quartiles) for τT were 666.1 (381.4–702.9) pg/ml, for Aβ42 were 341.7 (284.8–385) pg/ml and for τP-181 were 83.7 (60.8–104.7) pg/ml. Five patients (83%) showed the AD CSF biomarker profile (both τT and τP-181 increased and Aβ42 decreased) except for 1 patient (#5, 17%) with only Aβ42 decreased and both τT and τP-181 normal (Fig. 1). However, even the later patient showed increased (AD-like) τT/Aβ42 and τP-181/Aβ42 ratios. Three patients (50%) had increased CSF protein (range 57–74 mg/dL) and one of them had increased albumin index (10.1, normal values <9). None showed increased cell count. None had increased IgG index or positive oligoclonal bands.

c) Imaging findings

All patients had white matter (micro) ischemic lesions (Fig. 2). In 3 of them (50%) confluent lesions were more prominent in a posterior (parieto-occipital) location. In 2 patients (33%, #5, 6) lesions were compatible with relatively larger infarcts. Five patients (83%) had cortical/sub cortical micro bleeds and 1 of them (17%) had a recent lobar hemorrhage, while 2 (33%) had evidence of small previous hemorrhages. Two patients (33%) had cortical superficial siderosis (cSS). Four patients (67%) showed some degree of hippocampal atrophy. None of the patients showed gadolinium enhancing lesions.

Figure 1: Scatter plots of CSF biomarker levels of the studied patients. Horizontal bars indicate median values and horizontal broken lines indicate cut-off values of our laboratory [15]. The filled black circle indicates the patient with abnormal value only for Aβ42.
Figure 2: Imaging findings of the studied patients.
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Figure 2
Imaging findings of the studied patients.

Patient 1: (a) Computerized scan (CT) of lobar hemorrhage at 15 days and (b) MRI (T1) at 17 days; (c) Fluid attenuated inversion recovery (FLAIR) image showing white matter lesions (WMLs) with “posterior preference” and (d) T2* image showing corticosubcortical microbleeds.

Patient 2: (e,f) FLAIR images showing WMLs with “posterior preference”; (g,h) T2* images showing corticosubcortical microbleeds.

Patient 3: (i) T1 image showing mild hippocampal atrophy; (j) FLAIR image with WMLs and (k) susceptibility weighted image (SWI) with microbleeds, both of which show “posterior preference”.

Patient 4: (l) FLAIR and (m) SWI image showing WMLs and microbleeds respectively.

Patient 5: (n,o,p) T2* images showing cortical superficial siderosis (cSS) and some microbleeds and/or remnants of an old corticosubcortical small hemorrhage in the left parietal lobe (hippocampal atrophy is also present); (q) FLAIR image showing WMLS and ischemic lesions in the left anterior frontal lobe.

Patient 6: (r) T2 image showing hippocampal atrophy; (s,t) FLAIR images showing WMLs and an ischemic lesion in the left frontal lobe; (u) T2* image showing cSS and remnants of two old corticosubcortical hemorrhages (one in the left frontal and the other in the right parietal lobe).

Discussion
The present study is an observational study of patients with cognitive complaints seeking attention in a cognitive disorders tertiary clinic. These patients presumably had Aβ-related CAA, based on imaging (but not necessarily clinical) evidence of CAA [7] and low Aβ42 in the CSF. Five out of 6 patients had all three biomarkers (τT: Aβ42and τP-181) abnormal, thus showing the typical AD biomarker profile [17,18]. Even the patient having abnormal only the Aβ42, had abnormal τT/Aβ42 and τP-181/Aβ42 ratios [15,19,20], indicating that, practically all patients were compatible with the AD CSF biomarker profile.

Only one patient had a clinically evident hemorrhagic event (lobar hemorrhage). All others, despite imaging evidence of micro bleeds or previous subclinical hemorrhagic complications, belonged to the so-called “non-hemorrhagic” subtype of CAA, although such a distinction between “hemorrhagic” and “non-hemorrhagic” subtypes may not be accurate or important [8].

Only one of our patients showed the hippocampus amnestic type of dementia, typically expected in AD [11]. All others had mixed or atypical profiles with frontal-sub cortical, visuospatial, language and psychiatric-behavioral components. This is not surprising, since CAA, when present, adds an additional and independent component in the dementia of AD [21]. Many patients do not develop the typically expected episodic memory dysfunction [22], but a frontal-sub cortical type of impairment, including reduced processing speed and executive dysfunction [22–25]. Visuospatial dysfunction [26] or behavioral psychiatric symptoms [27] may be the predominant features in some patients. Indeed, in our cohort, two patients would otherwise receive the clinical diagnosis of FTD or DLB.

Ischemic events (TIAs, stroke) were observed in one patient and this is not unexpected since various types of ischemic lesions may be present in CAA [1]. On the other hand, micro bleeds in AD-related CAA may mimic TIAs [28]. Seizures were also observed in some patients. Epileptic seizures are commonly present in CAA-related inflammation [1]; however none of our patients had imaging or CSF evidence of an inflammatory response. Partial seizure-like stereotypical symptoms have been described in patients with focal (convexal) SH and AD-like CSF biomarkers [29]. It is possible that some of the symptoms attributed to TIA or simple partial seizures in our patients, could, in fact, represent transient focal neurological episodes (TFNEs), which may be caused by various mechanisms such as spreading depression and/or focal epileptic activity, they are associated with focal SH/cSS and some of which may respond to antiepileptic treatment [1,8,30].

In conclusion, patients with Aβ-related CAA presenting in cognitive disorder departments seem to have a low percentage of clinically evident hemorrhagic events and a high percentage of dementia with a non-amnestic profile.

References
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