Symbiosis

www.symbiosisonline.org
www.symbiosisonlinepublishing.com

Research Article | International Journal of Alzheimer's and Parkinson's Diseases | Open Access

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

George P. Paraskevas[1], Vasilios C. Constantinides[1], Anastasia Bougea[1], Panagiotis Paraskevas[2], Georgios Tsivgoulis[3], Elisabeth Kapaki[1*]

[1]1st Department of Neurology, Cognitive and Movement Disorders Clinic and Neurochemistry and Biological MarkersUnit, School of Medicine, National and Kapodistrian University of Athens, Eginition Hospital, Athens, Greece

[2]Technological Educational Institute of Crete, School of Health and Welfare Services, Nursing Department, Heraklion, Crete, Greece

[3]2nd Department of Neurology, Medical School, National and Kapodistrian University of Athens, Attikon Hospital, Athens, Greece

Received: November 19, 2018; Accepted: November 30, 2018; Published: December 14, 2018

***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 1or 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 Aβwith 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/corticosubcorticalmicrobleeds, 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 corticosubcortical 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 corticisubcortical 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 andvisuoconstructive 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 Eginition 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 ("InnotesthTau 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].

Neuroimaging

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 (TIAs) and ischemic 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

Table 1: Demographic, clinical, imaging and biochemical data of the studied patients

#Sex	Age (y)	Risk factors and family hisotry	Presenting symptom(s)	Accompanying or later symptom(s)	CSF	Imaging
1F	64	Hypertension	At age 64 left frontal lobar hemorrhage	Frontal MCI and significant anxiety-depression	**τT↑, τP-181↑, Aβ42↓**	WMLs, lobar hemorrhage, microbleeds
					Otherwise normal	
2F	78	Hypetension.	Generalized seizures starting at age 75, responding well to oxcarbazepine.	At age 76 MCI. Now, mild non-amnestic dementia with frontal and especially visuoconstructive components.	**τT↑, τP-181↑, Aβ42↓**	WMLs, mild hippocampal atrophy, microbleeds
		APOE:ε3/ε4.	EEG: diffuse slowing and bilateral theta and delta waves	Bilateral pyramidal signs with no gait difficulty	Otherwise normal	
		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
		Sister with history of stroke and dementia			Otherwise normal	
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
				At age 77 MCI. Now mixed type dementia (frontal, memory, and especially visuo-constructive)		
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
				EEG: generalized slowing and theta or delta waves	albumin index↑	
				Mild parkinsonian signs		

M: male, F: female, y: years, CSF: cerebrospinal fluid, MCI: mild cognitive impairment, WMLs: white matter lesions, TIAs: transient ischemic attacks, cSS: cortical superficial siderosis, EEG: electroencephalogram.

on and, thus, at least MCI and usually dementia always developed during the disease process. Four patients (#2,3,4,6,67%) developed pyramidal and/or parkinsonian signs during the disease process, sometimes with gait difficulty. Significant depression was present in 2 patients (#2,4, 33%)

Dementia was of theamnestic 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 ADwith 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 probablebvFTD [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 τTand τP-181 increased and Aβ42 decreased) except for 1 patient (#5, 17%) with only Aβ42 decreased and both τTand 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.

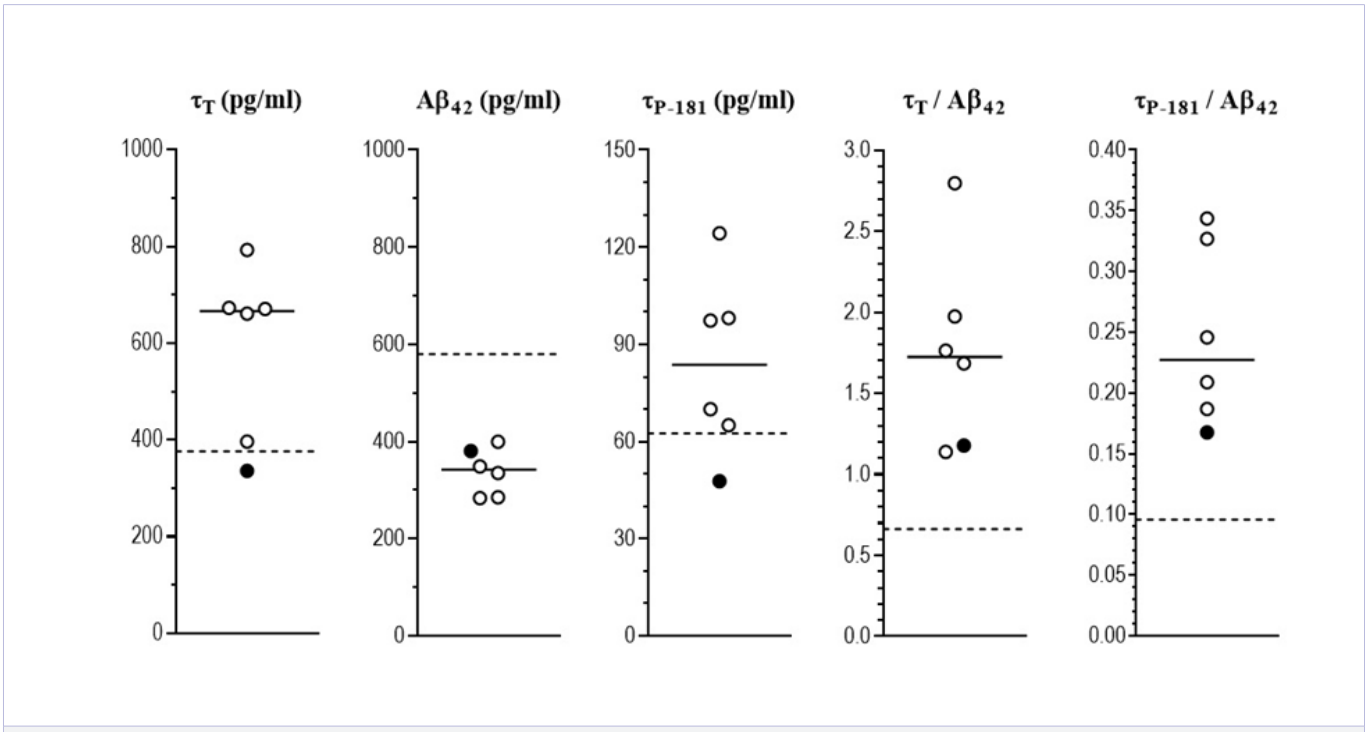

Figure 1: Scatter plots of CSF biomarker levels of the studied patients. Horizontal bars indicate median values and horizontal broken lines indicate cut-off values of our laboratory [15]. The filled black circle indicates the patient with abnormal value only for $A\beta_{42}$.

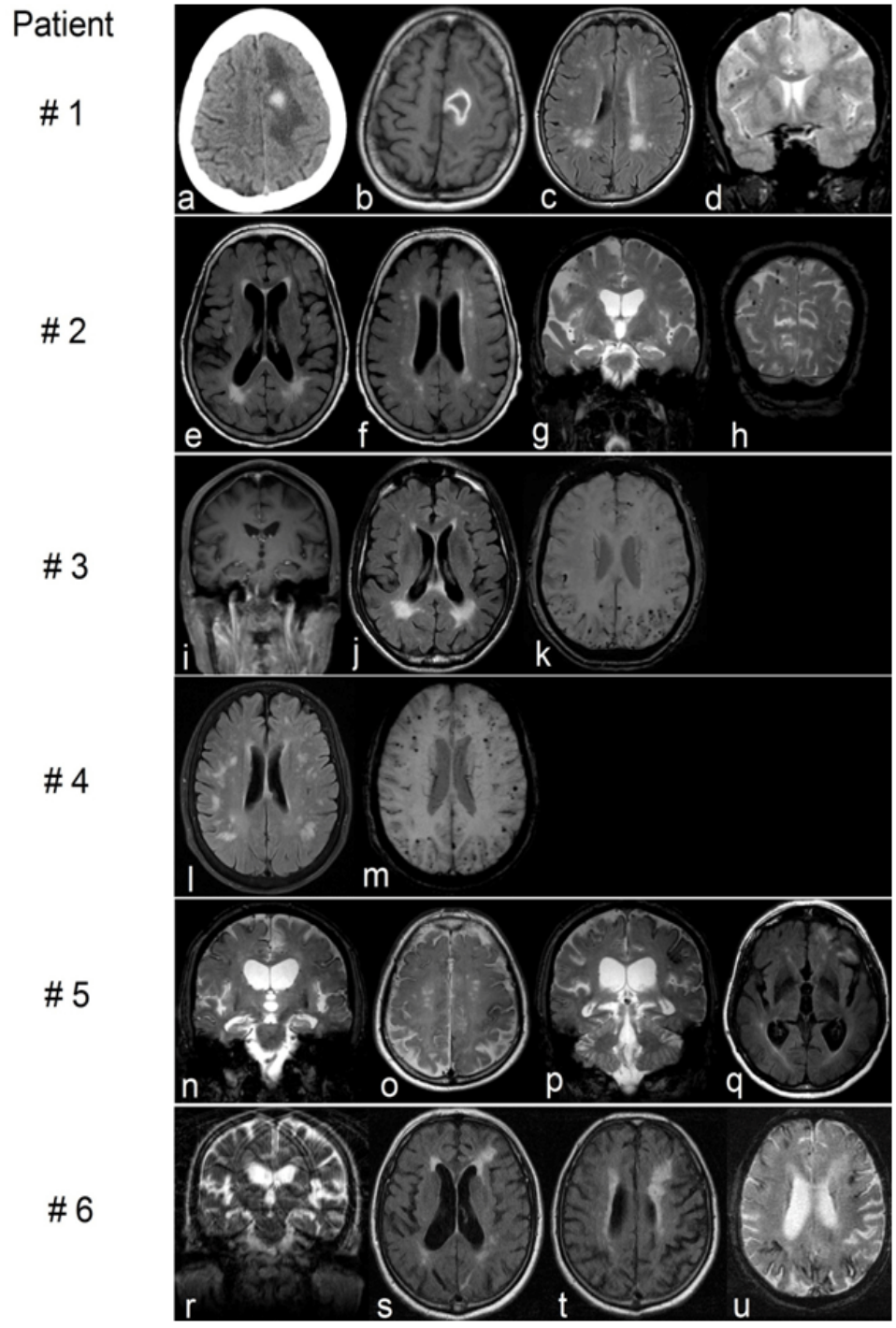

Figure 2: Imaging findings of the studied patients.

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 corticosubcorticalmicrobleeds.

Patient 2: (e,f) FLAIR images showing WMLs with "posterior preference"; (g,h) T2* images showing corticosubcorticalmicrobleeds.

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 microbleedsand/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 TIAsor simple partial seizures in our patients, could, in fact, represent transient focal neurological episodes (TFNEs), which may be caused may 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

1. Yamada M. Cerebral amyloid angiopathy: emerging concepts. J Stroke. 2015;17(1):17–30.
2. Yamada M. The spectrum of cerebral amyloid angiopathy-related disorders. Intern Med. 2014;53(17):1893–1894.
3. Yamada M. Predicting cerebral amyloid angiopathy-related intracerebral hemorrhages and other cerebrovascular disorders in Alzheimer's disease. Front Neurol. 2012;3:64.
4. Attems J, Jellinger KA. The overlap between vascular disease and Alzheimer's disease–lessons from pathology. BMC Med. 2014;12:206. doi:10.1186/s12916-014-0206-2
5. Jellinger KA, Attems J. Neuropathological evaluation of mixed dementia.J Neurol Sci. 2007;257 (1-2):80–87.
6. Salvarani C, Morris JM, Giannini C, Brown RD Jr, Christianson T, Hunder GG. Imaging Findings of Cerebral Amyloid Angiopathy, Aβ-Related Angiitis (ABRA), and Cerebral Amyloid Angiopathy-Related Inflammation: A Single-Institution 25-Year Experience. Medicine (Baltimore). 2016;95(20). doi: 10.1097/MD.0000000000003613

7. Linn J, Halpin A, Demaerel P, Ruhland J, Giese AD, Dichgans M, van Buchem MA, Bruckmann H, et al. Prevalence of superficial siderosis in patients with cerebral amyloid angiopathy. Neurology. 2010;74(17):1346-50. doi:0.1212/WNL.0b013e3181dad605

8. Banerjee G, Carare R, Cordonnier C, Greenberg SM, Schneider JA, Smith EE, et al. The increasing impact of cerebral amyloid angiopathy: essential new insights for clinical practice. J NeurolNeurosurg Psychiatry. 2017;88(11):982–994. doi: 10.1136/jnnp-2016-314697

9. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR Jr, Kawas CH, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's Dement. 2011;7(3):263–269. doi:10.1016/j.jalz.2011.03.005

10. Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's Dement. 2011;7:270–279. doi:10.1016/j.jalz.2011.03.008

11. Dubois B, Feldman HH, Jacova C, Hampel H, Molinuevo JL, Blennow K, et al. Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. Lancet Neurol. 2014;13(6):614–629. doi:10.1016/S1474-4422(14)70090-0

12. McKeith IG, Boeve BF, Dickson DW, Halliday G, Taylor JP, Weintraub D, et al. Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. Neurology. 2017;89(1):88–100. doi:10.1212/WNL.0000000000004058

13. Rascovsky K, Hodges JR, Knopman D, Mendez MF, Kramer JH, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain. 2011;134:2456–2477. doi:10.1093/brain/awr179

14. Del Campo M, Mollenhauer B, Bertolotto A, Engelborghs S, Hampel H, Simonsen AH, et al. Recommendations to standardize preanalytical confounding factors in Alzheimer's and Parkinson's disease cerebrospinal fluid biomarkers: an update. Biomark Med. 2012;6(4):419–430. doi:10.2217/bmm.12.46

15. Paraskevas GP, Kaselimis D, Kourtidou E, Constantinides V, Bougea A, Potagas C, et al. Cerebrospinal Fluid Biomarkers as a Diagnostic Tool of the Underlying Pathology of Primary Progressive Aphasia. J Alzheimers Dis. 2017;55(4):1453–1461. doi:10.3233/JAD-160494

16. Bourbouli M, Kapaki E, Petropoulou O, Paraskevas GP. Improved Performance of CSF Dementia Biomarker Measurements Over Time: The Effect of Quality Control and Harmonization Programs. BiomarkApplic. 2018:2. doi:10.29011/BMAP-126. 100026

17. Paraskevas GP, Kapaki E, Papageorgiou SG, Kalfakis N, Andreadou E, Zalonis I, et al. CSF biomarker profile and diagnostic value in vascular dementia. Eur J Neurol. 2009;16(2):205-211. doi:10.1111/j.1468-1331.2008.02387.x

18. Simonsen AH, Herukka SK, Andreasen N, Baldeiras I, Bjerke M, Blennow K, et al. Recommendations for CSF AD biomarkers in the diagnostic evaluation of dementia. Alzheimer's Dement. 2017;13(3):274–284.

19. Kapaki E, Liappas I, Paraskevas GP, Theotoka I, Rabavilas A. The diagnostic value of tau protein, beta-amyloid (1-42) and their ratio for the discrimination of alcohol-related cognitive disorders from Alzheimer's disease in the early stages. Int J Geriatr Psychiatry. 2005;20(8):722–729.

20. Kapaki E, Paraskevas GP, Zalonis I, Zournas C. CSF tau protein and beta-amyloid (1-42) in Alzheimer's disease diagnosis: discrimination from normal ageing and other dementias in the Greek population. Eur J Neurol. 2003;10(2):119–128.

21. Boyle PA, Yu L, Nag S, Leurgans S, Wilson RS, Bennett DA, et al. Cerebral amyloid angiopathy and cognitive outcomes in community-based older persons. Neurology. 2015;85(22):1930–1936. doi:10.1212/WNL.0000000000002175

22. Case NF, Charlton A, Zwiers A, Batool S, McCreary CR, Hogan DB, et al. Cerebral Amyloid Angiopathy Is Associated With Executive Dysfunction and Mild Cognitive Impairment. Stroke. 2016;47(8):2010–2016. doi:10.1161/STROKEAHA.116.012999

23. Xiong L, Davidsdottir S, Reijmer YD, Shoamanesh A, Roongpiboonsopit D, et al. Cognitive Profile and its Association with Neuroimaging Markers of Non-Demented Cerebral Amyloid Angiopathy Patients in a Stroke Unit. J Alzheimers Dis. 2016;52(1):171–178. doi:10.3233/JAD-150890

24. Gregoire SM, Scheffler G, Jäger HR, Yousry TA, Brown MM, Kallis C, et al. Strictly lobar microbleeds are associated with executive impairment in patients with ischemic stroke or transient ischemic attack. Stroke. 2013;44(5):1267–1272. doi:10.1161/STROKEAHA.111.000245

25. Gregoire SM, Smith K, Jäger HR, Benjamin M, Kallis C, et al. Cerebral microbleeds and long-term cognitive outcome: longitudinal cohort study of stroke clinic patients. Cerebrovasc Dis. 2012;33(5):430–435. doi:10.1159/000336237

26. Chung CP, Chou KH, Chen WT, Liu LK, Lee WJ, Chen LK, et al. Strictly Lobar Cerebral Microbleeds Are Associated With Cognitive Impairment. Stroke. 2016;47(10):2497–2502. doi:10.1161/STROKEAHA.116.014166

27. Gleason A, Hayhow B, Emmanuel J, Gaillard F. Cerebral amyloid angiopathy presenting with neuropsychiatric symptoms. Aust N Z J Psychiatry. 2014;48(8):779–780. doi:10.1177/0004867414525843

28. Safouris A, Gazagnes MD, Triantafyllou N, Tsivgoulis G. Cerebral amyloid angiopathy-associated microbleed mimicking transient ischemic attack. J Neurol Sci. 2015;351(1-2):198–199. doi:10.1016/j.jns.2015.02.032

29. GarcíaEstévez DA, García-Dorrego RM, Nieto-Baltar B, Marey-Garrido M, Hierro-Torner T. Spontaneous convexity subarachnoid haemorrhage: Clinical series of 3 patients with associated cerebral amyloid angiopathy. Neurologia. 2017;32(4):213–218. doi:10.1016/j.nrl.2015.11.004

30. Charidimou A, Peeters A, Fox Z, Gregoire SM, Vandermeeren Y, Laloux P, et al. Spectrum of transient focal neurological episodes in cerebral amyloid angiopathy: multicentre magnetic resonance imaging cohort study and meta-analysis. Stroke. 2012;43(9):2324–2330. doi:10.1161/STROKEAHA.112.657759