

β -amyloid deposits in veins in patients with cerebral amyloid angiopathy and intracerebral haemorrhage

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Abstract

Aim of the study: To review the incidence and grade of cerebral amyloid angiopathy (CAA) in veins in patients who died due to spontaneous intracerebral haemorrhage (ICH).

Material and methods: Neuropathological examinations were performed in the study group of 189 patients. Cerebral amyloid angiopathy was diagnosed according to the Boston criteria and confirmed during an autopsy. The Vonsattel and Mountjoy scales were used to assess the grade and scores of CAA.

Results: In the study group composed of 189 ICH patients, 42 presented CAA. In the microscopic examination, of the 42 patients 33 (78%) showed β -amyloid deposits in veins, which makes 17% of the total group of patients with ICH. In this group, the age ranged from 54 to 97 (mean age 80.18 ± 8.15 years). A group of 33 (27 women and 6 men) patients comprised 15 (45%) patients with severe CAA, 13 (40%) with moderate and 5 (15%) with mild CAA classified according to the Vonsattel scale. According to the Mountjoy scale 28 (85%) patients had a score of 4, which indicated the total involvement of the vessel.

Conclusions: β -amyloid deposits in veins were found in 78% of patients with CAA and ICH, which makes 17% of the total group of patients with ICH. Interestingly, β -amyloid deposits in veins are not so rare in patients with CAA who died due to intracerebral haemorrhage. Cerebral amyloid angiopathy localization in the veins of the brain was observed more frequently than previously suspected. Veins may play a role in the elimination of β -amyloid from the brain.

Key words: cerebral amyloid angiopathy (CAA), β -amyloid, veins, intracerebral haemorrhage (ICH).

Introduction

Cerebral amyloid angiopathy (CAA), also known as congophilic amyloid angiopathy, is a progressive degenerative disease in which protein β -amyloid is deposited in the leptomeningeal and brain cortical small- and middle-sized arteries, veins and capillary walls. Cerebral amyloid angiopathy is the second cause of brain haemorrhage after atherosclerosis. It can also cause ischemic strokes, transient ischemic attacks, leukoencephalopathy, brain tumour (amyloidoma) and

inflammatory vasculitis ($A\beta$ -related angiitis). Cerebral amyloid angiopathy coexists with Alzheimer's disease (AD), dementia with Lewy bodies, Down syndrome and many other dementia-inducing disorders [1-4,7,13,17, 18,21,22]. In cerebral amyloid angiopathy, intracerebral haemorrhages (ICH) are superficial, multiple and occur in older people mostly with no history of hypertension [7,16]. The incidence of spontaneous cerebral amyloid angiopathy becomes more common with the increasing age; from 2.3% to 22% at the age of 65 and

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from 70% to 100% over the age of 80 years with a prevalence in AD (78-100%) [12]. The prevalence of CAA in intracerebral haemorrhages ranged from 2.0% to 23% [12]; 30-40 cases of CAA per 100,000 population have been recorded annually [7].

Cerebral veins are rarely involved in β -amyloid [25]. There are no publications concerning the involvement of veins in CAA in ICH. The aim of the study was to assess the incidence and grade of CAA in the veins of patients who died due to spontaneous ICH.

Material and methods

All patients were hospitalized in the 2nd Department of Neurology, Institute of Psychiatry and Neurology, Warsaw, Poland. The study group consisted of patients who died due to spontaneous intracerebral haemorrhages in 1993-2012. The final diagnosis was made during an autopsy following histological and immunohistological examinations according to the Boston criteria [15].

Patients with suspected ICH were admitted to our hospital. They were hospitalized in the Stroke Unit. Over 20 years 189 patients died due to intracerebral haemorrhage of whom 42 were postmortem diagnosed with CAA. CAA was confirmed during a neuropathological examination. In 33 cases, veins were affected by CAA. Patients with brain aneurysm, arteriovenous malformation, brain tumour, venous thrombosis, haemophilias, past head injury, as well as those on anticoagulants and thrombolytic therapy were excluded.

The autopsy was performed according to the standard protocol. The brain was fixed in 4% paraformaldehyde in 0.1 M phosphorane-buffer saline and embedded in paraffin. Then, it was sliced coronally. The specimens were stained with H&E, PAS, Congo red and immunohistochemically with the two antibodies: anti A β 8-17 (DAKO, 1 : 50) and actin (SMA, DAKO, 1 : 50).

Under the microscopic evaluation the brain was considered positive for CAA when it showed at least one leptomeningeal or cortical congophilic vessel with yellow-green birefringence under polarized light and/or β -amyloid deposits were seen within the wall of the vessels. The severity of CAA was classified according to the Vonsattel scale (Fig. 1):

- 1) mild – deposits of β -amyloid are restricted to a congophilic rim around normal or atrophic smooth muscle fibers (which might be absent), leaving an optically empty tiny vacuole-like zone surrounded by amyloid, in media of otherwise normal vessels,
- 2) moderate – media is replaced by β -amyloid and thicker than normal, with no evidence of remote or recent blood leakage,

- 3) severe – there are extensive β -amyloid deposits with focal wall fragmentation and at least one focus of perivascular leakage evidenced by the presence of erythrocytes or hemosiderin or both [24].

The estimated proportion of β -amyloid involvement in each vessel was recorded according to the Mountjoy scale (Fig. 2). A score of 0 indicated the absence of amyloid; a score of 1 – involvement of up to one-quarter of the vessel circumference; a score of 2 – involvement of up to one-half of the vessel circumference; a score of 3 – involvement of up to three-quarters of the vessel circumference; and a score of 4 indicated total involvement of the vessel [19].

Results

The results of the study focused on the clinical and neuropathological findings in cerebral amyloid angiopathy in patients who died due to spontaneous intracerebral haemorrhages are presented.

Deposits of β -amyloid CAA were observed in all kinds of cerebral vessels, arteries (cortical and meningeal), capillaries and veins. The neuropathological features localized in veins are presented in Table I.

In the group of 189 patients with ICH, we found 42 patients with CAA. In the CAA group, we revealed 33 (78%) patients with β -amyloid deposits in veins, which made 17% of the total group of patients who died due to ICH. In this group, there were 27 women and 6 men; their age ranged from 54 to 97 (mean age 80.18 ± 8.15 years).

The grade of CAA according to the Vonsattel scale is presented in Table II. The following grades were identified: severe CAA in 15 (45%) patients, moderate in 13 (40%) and mild CAA in 5 (15%) patients. According to the Mountjoy scale, we found score 4 in 28 (85%) patients, score 3 in 3 (9%), score 2 in 1 (3%) and score 1 in 1 (3%) patient (Table III).

We found one patient with Down syndrome and ICH who had veins involved with severe CAA and one patient suffering from dementia with Lewy bodies and ICH who had veins involved with moderate CAA.

Discussion

To our best knowledge, there are no reports on the veins involvement in CAA or ICH. Therefore, we tried to find out how often the brain veins are deposited by β -amyloid.

Neuropathological examination is still a “gold standard” for CAA diagnosis. Using the Boston criteria for

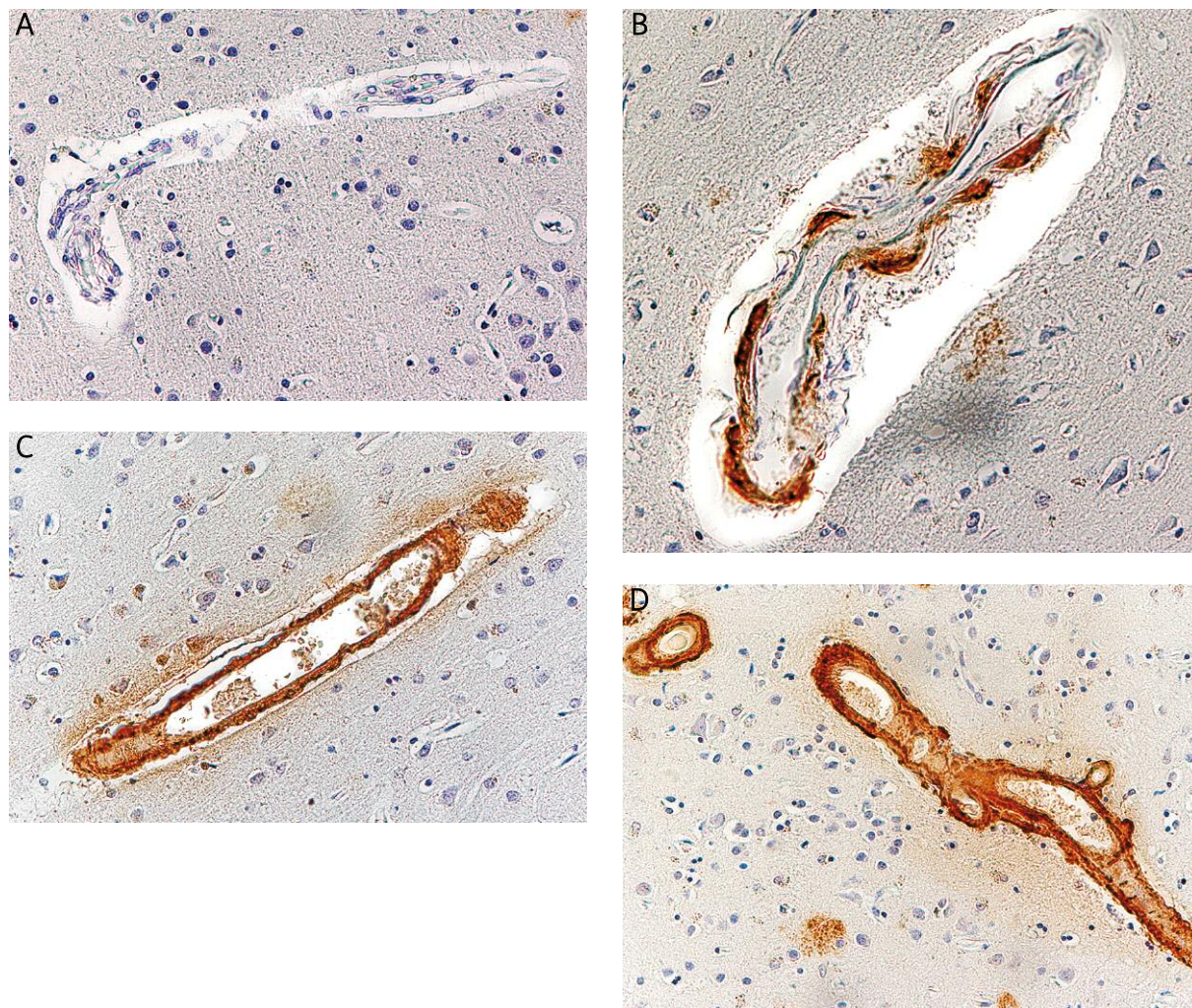


Fig. 1 The severity of CAA according to the Vonsattel scale was classified as follows: **A)** normal vein, without deposits of β -amyloid. β -amyloid. x 200; **B)** 1. Mild – β -amyloid is restricted to segmental β -amyloid depositions. β -amyloid. x 200; **C)** 2. Moderate – Media is replaced by β -amyloid and is thicker than normal, with no evidence of remote or recent blood leakage. β -amyloid. x 200; **D)** 3. Severe – there is extensive amyloid deposition with focal wall fragmentation and focus of perivascular leakage. β -amyloid. x 200.

CAA diagnosis and having CT and/or MRI scans the neurologist may select those of the patients whom he or she most suspects of having CAA [6,8,9,11,14,15,20,23]. Also positron emission tomography (PET) scans can be used in the diagnosis of β -amyloid deposition in the brain [5].

A definite diagnosis of CAA can be made through a postmortem examination or obtained via intracranial biopsy, while on the basis of clinical data, and CT or MRI scans of the brain, CAA can be only suspected [7,10,15,19,24].

There is a lot of diagnostic tools which can be used in the diagnosis of CAA during intracerebral haemorrhage, but only neuropathological examination can confirm the presence of this disease and reveal CAA stages, as well as the kinds of vessels involved in this process. It can allow to classify the grades and scores of CAA and its localization [7,10,15,19,24].

There are only a few ways to eliminate β -amyloid from the brain. Imbalance between β -amyloid production and clearance is generally considered a key element in the formation of amyloid deposits. The amphiphilic

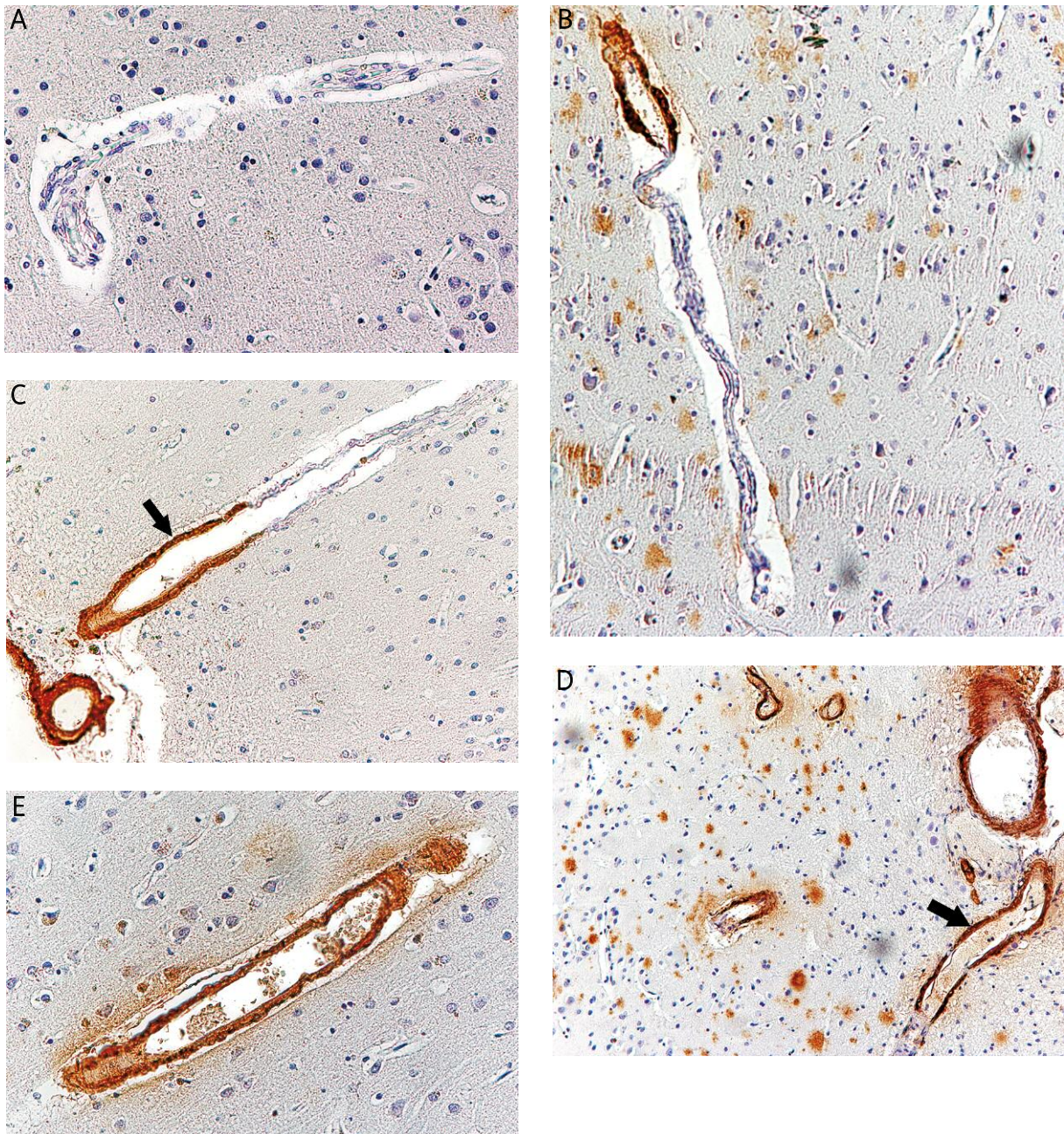


Fig. 2. The estimated proportion of amyloid involvement in each vessel was recorded according to the Mountjoy scale. **A)** A score of 0 indicated the absence of β -amyloid deposits. β -amyloid. x 200; **B)** A score of 1 – involvement of up to one-quarter of the vessel circumference. β -amyloid. x 100; **C)** A score of 2 – involvement of up to one-half of the vessel circumference (arrow). β -amyloid. x 200; **D)** A score of 3 – involvement of up to three-quarters of the vessel circumference (arrow). β -amyloid. x 100; **E)** A score of 4 – total involvement of the vessel. β -amyloid. x 200.

nature of β -amyloid precludes its crossing through the blood-brain barrier unless mediated by specialized carriers and/or receptor transport mechanisms. These mechanisms control the uptake of circulating β -amy-

loid into the brain and regulate clearance. Among receptors involved, receptor for Advance Glycation End-products actively participates in brain uptake of free β -amyloid at the vessel wall level. Other receptors are more

Table I. Cerebral amyloid angiopathy severity in veins of patients with intracerebral haemorrhages

Number/Initials	Age	Sex	CAA severity according to the Vonsattel scale	CAA severity according to the Mountjoy scale
1/WP	84	F	2	4
2/WP	85	F	2	4
3/RZ	87	F	1	3
4/AP	83	F	3	4
5/KT	97	F	2	4
6/BP	68	F	2	4
7/HW	72	F	1	3
8/TN	89	M	3	4
9/DK	80	F	2	4
10/SP	68	M	2	4
11/ZO	89	F	2	4
12/RB	77	F	3	4
13/SD	84	M	1	2
14/AP	87	F	3	4
15/AWZ	72	F	3	4
16/EC	89	M	2	4
17/PW	54	F	3	4
18/SO	78	F	2	4
19/JZ	85	M	3	4
20/MK	82	F	3	4
21/AO	77	F	3	4
22/RS	79	F	3	4
23/MSG	79	F	3	4
24/JF	81	F	3	4
25/HK	79	F	1	3
26/MM	75	F	3	4
27/EK	67	F	2	4
28/SZ	91	F	3	4
29/JP	88	F	2	4
30/HG	71	M	2	4
31/AR	84	F	1	1
32/KM	77	F	3	4
33/WR	88	F	2	4

Table II. Cerebral amyloid angiopathy grades according to the Vonsattel scale

CAA grade	Number (%)
Mild	15 (45%)
Moderate	13 (40%)
Severe	5 (15%)

relevant to the transport of β-amyloid complexed with other molecules: low-density-lipoprotein receptor related protein-1 (LRP-1) mediated transcytosis of β-amyloid-ApoE complexes contributing to rapid CNS clearance, whereas megalin mediates the cellular uptake and transport of β-amyloid-ApoJ. Neprilysin, endothelin-amyloid-converting enzyme, insulin-degrading enzyme, beta-amyloid-converting enzyme 1, plasmin and matrix metalloproteases are among major enzymes known to participate in brain β-amyloid catabolic pathways. Reduced levels and/or activity of β-amyloid degrading enzymes favour β-amyloid accumulation causing increased levels of β-amyloid deposits. β-amyloid can be also eliminated from the brain by the perivascular drainage. There is no evidence that all these receptors are located in all kinds of cerebral vessels [3].

Brain veins localized in the grey and white matter have a relatively large lumen and thin walls that lack smooth muscle cells. This characteristic distinguishes veins from arteries. The leptomeningeal cells around veins do not form a complete sheath and there is a perivascular space around veins containing a few collagen fibers. Postcapillary venules are the site for the receptor-mediated entry of inflammatory cells into the brain [25].

According to Weller *et al.* (2009), veins do not appear to be involved in CAA, although deposits of β-amyloid are found attached to the walls of veins [25].

In our microscopic findings, we found veins involved in 33 (78 %) patients. According to both Vonsattel and Mountjoy scales, severe and moderate changes were dominating in our group of patients. Based on our results we may assume that veins may play a more important role in β-amyloid elimination from the brain than we previously thought.

Conclusions

We found β-amyloid deposited in veins in 78% of patients with CAA and ICH. Veins are not so rarely in-

Table III. Cerebral amyloid angiopathy scores according to the Mountjoy scale

CAA score	Number (%)
1	1 (3%)
2	1 (3%)
3	3 (9%)
4	28 (85%)

volved in β-amyloid in intracerebral haemorrhage. Cerebral amyloid angiopathy was localized in brain veins more often than we previously suspected. Veins may play an important role in the elimination of β-amyloid and not only as a perivascular drainage.

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