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Original Article

Characterization of cerebellar amyloid-β deposits in Alzheimer disease

Gianluca Lopez, MD[1,2,3,*], Shino D. Magaki, MD, PhD[1], Christopher Kazu Williams[1], Annlia Paganini-Hill, PhD[4], Harry V. Vinters, MD[1,5]

[1]Section of Neuropathology, Department of Pathology and Laboratory Medicine, Ronald Reagan UCLA Medical Center and David Geffen School of Medicine, University of California, Los Angeles, California, USA
[2]Department of Biomedical, Surgical and Dental Sciences, University of Milan, Milan, Italy
[3]Division of Pathology, Fondazione IRCCS Ca' Granda—Ospedale Maggiore Policlinico, Milan, Italy
[4]Department of Neurology, University of California, Irvine, Irvine, California, USA
[5]Department of Neurology, Ronald Reagan UCLA Medical Center and David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, California, USA

*Send correspondence to: Gianluca Lopez, MD, Department of Biomedical, Surgical and Dental Sciences, University of Milan, Via della Commenda 10, 20122, Milan, Italy; E-mail: gianluca.lopez@unimi.it

ABSTRACT

Cerebellar amyloid-β (Aβ) plaques are a component of the diagnostic criteria used in Thal staging and ABC scoring for Alzheimer disease (AD) neuropathologic change. However, Aβ deposits in this anatomic compartment are unique and under-characterized; and their relationship with other pathological findings are largely undefined. In 73 cases of pure or mixed AD with an A3 score in the ABC criteria, parenchymal (plaques) and vascular (cerebral amyloid angiopathy [CAA]) cerebellar Aβ-42 deposits were characterized with respect to localization, morphology, density, and intensity. Over 85% of cases demonstrated cerebellar Aβ-42 parenchymal staining that correlated with a Braak stage V-VI/B3 score ($p < 0.01$). Among the 63 with cerebellar Aβ-42 deposits, a diffuse morphology was observed in 75% of cases, compact without a central dense core in 32%, and compact with a central dense core in 16% (all corresponding to plaques evident on hematoxylin and eosin staining). Cases with Purkinje cell (PC) loss showed higher proportions of PC layer Aβ-42 staining than cases without PC loss (88% vs 44%, $p = 0.02$), suggesting a link between Aβ-42 deposition and PC damage. Among all 73 cases, CAA was observed in the parenchymal vessels of 19% of cases and in leptomeningeal vessels in 44% of cases.

KEYWORDS: Aβ, Aβ-42, Alzheimer disease, Amyloid, Cerebellum, Plaque

INTRODUCTION

Cerebellar amyloid-β (Aβ) deposits are diagnostic criteria for Thal phase 5 and fulfill criteria for an A3 score in the National Institute on Aging-Alzheimer's Association (NIA-AA) ABC scoring system for evaluating Alzheimer disease (AD) neuropathologic change (1–4). Cerebellar Aβ plaques are usually diffuse and seen in advanced stages of AD (5, 6), typically at a lower density compared with plaques in the cerebral cortex (7), possibly due to increased Aβ clearance in the cerebellum (8). Notably, Aβ deposition in the cerebellum is also increased in older persons without dementia, similar to other brain areas in which Aβ density increases with age (9). In contrast to diffuse plaques, cerebellar neuritic plaques and dystrophic neurites have been rarely observed in sporadic AD (3), and are best evaluated with anti-ubiquitin antibodies (10), silver stains (11) or at an ultrastructural level (12). Cerebellar neurofibrillary tangles, along with hyperphosphorylated tau, have been observed in cases of familial AD but are usually not seen in sporadic AD (6, 13–15).

It has been suggested that cerebellar dysfunction may occur in the early stages of AD, independent of extracellular Aβ plaque accumulation, due to alterations in intracellular amyloid precursor protein (APP) processing (16). Compared with healthy controls, APP is increased in the cerebellum of AD patients without Aβ deposits (17). However, preclinical models show that different subtypes of Aβ can cause granule cell apoptosis (18), and disrupt parallel fiber signaling via a pro-inflammatory process (19). Although Aβ deposition has not been associated with morphologically evident Purkinje cell (PC) damage (20), a small number of degenerating neurites among diffuse plaques have been observed by electron microscopy (12, 19). Additionally, the prevalence, severity, and density of cerebral amyloid angiopathy (CAA) in the cerebellum of AD patients have seldom been described, with only Braak et al reporting CAA in the majority of Down syndrome (9/10, 90%) and AD (7/8, 87%) patients (6). Recently, it was reported that nearly half of post-mortem cases with occipital CAA have concomitant cerebellar CAA (29/60, 48%) (21);

however, that study does not specify if the patients had a history of dementia or other AD-associated changes. A case of CAA-related cerebellar hemorrhage was reported in a patient with AD (22). Imaging studies show more cerebellar atrophy in non-AD patients with CAA than in AD patients without CAA or in healthy controls (23). No significant differences in the amount and subtypes of cerebellar Aβ deposits (extracellular, vascular, and perivascular) were noted between familial (*APP* V717I) and sporadic AD (24). Two studies that assessed Aβ-40 and Aβ-42/43 deposition with immunohistochemistry (IHC), using BA27 and BC05 antibodies, respectively, in the cerebellum of AD patients found Aβ-42 to be the major component of cerebellar Aβ deposits (25, 26). Notably, by using the 6E10 Aβ antibody, raised against Aβ1 − 17 and which also reacts with APP (27), the apparent prevalence of diffuse plaques in the cerebellum of AD patients is markedly reduced (6%) (28).

This study aims to assess the prevalence, density, localization, and morphology of Aβ-42 parenchymal and vascular deposits in the cerebellum of AD cases and to correlate such characteristics with other pathological findings.

MATERIALS AND METHODS

All autopsies performed between 2014 and 2022 at Ronald Reagan UCLA Medical Center, Los Angeles, CA were screened to identify cases with neuropathological changes of AD. Those with an A3 score according to the ABC criteria for AD (2), which corresponds to a Thal phase 4/5, were included in this study in order to assess all cases with advanced Aβ pathology. Sections of cerebellar cortex sectioned perpendicular to the folia and including the dentate nucleus (4) were stained with hematoxylin and eosin (H&E) and immunostained using primary antibodies against Aβ-42 (1:150, EMD Millipore, Burlington, MA, rabbit polyclonal, AB5078P). The slides were simultaneously reviewed on a multi-head microscope by HVV, SDM, and GL with consensus. We focused on Aβ42 since it possesses a higher sensitivity for parenchymal Aβ deposits than Aβ40 (29) and performed Aβ42 immunostaining in all cerebellar samples. PC loss was scored as absent, focal, or multifocal. The Aβ-related parameters were assessed and scored as: (1) localization of Aβ-42 deposition in the molecular, PC, or granular layer of the cerebellum: (2) morphology of Aβ-42 deposits, defined as diffuse,

Table 1. Clinicopathological characteristics of AD cases with an A3 score according to the NIA-AA ABC criteria

			All (%)	**Parenchymal Aβ-42 positive (%)**	**Parenchymal Aβ-42 negative (%)**
N			73 (100)	63 (86)	10 (13)
Age (years), mean ± SD			75.1 ± 10.6	75.2 ± 10.9	74.6 ± 8.3
Males/females			37 (51)/36 (49)	31 (49)/32 (51)	6 (60)/4 (40)
Brain weight (g), mean ± SD			1159.4 ± 163.9	1152.2 ± 164.5	1204.5 ± 152.5
Braak stage		III	1 (1)	0	1 (10)
		IV	3 (4)	1 (2)	2 (20)
		V	5 (7)	2 (3)	3 (30)
		VI	64 (88)	60 (95)	4 (40)
Aβ-42	Localization, layer	Molecular	53 (73)	53 (84)	0
		Purkinje cell	31 (43)	31 (49)	0
		Granular	22 (30)	22 (35)	0
	Morphology	Diffuse	47 (64)	47 (75)	0
		Compact	20 (27)	20 (32)	0
		Cored	10 (14)	10 (16)	0
	Density	Absent	10 (14)	0	10 (100)
		Focal	16 (22)	16 (25)	0
		Multifocal	21 (29)	21 (33)	0
		Widespread	26 (36)	26 (41)	0
	Intensity	Absent	10 (14)	0	10 (100)
		Mild	7 (10)	7 (11)	0
		Moderate	25 (34)	25 (40)	0
		Strong	31 (43)	31 (49)	0
CAA	Parenchymal	Absent	59 (81)	52 (83)	7 (70)
		Arteriolar only	1 (1)	0	1 (10)
		Capillary only	4 (5)	3 (5)	1 (10)
		Both	9 (12)	8 (13)	1 (10)
	Meningeal	Absent	40 (55)	33 (52)	7 (70)
		Scant	5 (7)	4 (6)	1 (10)
		Occasional	20 (27)	18 (29)	2 (20)
		Widespread	8 (11)	8 (13)	0
Plaque formation		No	63 (86)	53 (84)	0
		Yes	10 (14)	10 (16)	0
Purkinje cell loss		Absent	64 (88)	55 (87)	9 (90)
		Focal	5 (7)	5 (8)	0
		Multifocal	4 (6)	3 (5)	1 (10)

AD, Alzheimer disease; NIA-AA, National Institute on Aging-Alzheimer's Association; SD, standard deviation; CAA, cerebral amyloid angiopathy.

compact, or cored; (3) density of Aβ-42 deposits, scored as absent, focal, multifocal, or widespread; (4) intensity of Aβ-42 staining, scored as absent, mild, moderate, or strong; (5) parenchymal CAA assessed as absent, arteriolar only, capillary only, or both; (6) meningeal CAA, scored as absent, scant Aβ deposition, occasional circumferential Aβ deposition, or widespread circumferential Aβ deposition according to the protocol by Love et al (30). Other relevant histopathological findings (e.g. cerebellar microinfarcts) were also recorded.

IHC workup for co-pathology assessment was part of the initial neuropathologic evaluation for neurodegenerative diseases in our cohort. Lewy body disease was assessed based on both IHC for α-synuclein and histologic analysis on H&E. For cases with suspicion of TDP-43-related pathology, TDP-43 IHC was also performed.

Data are presented as mean ± standard deviation (SD) for continuous variables and number and percent for categorical variables. Differences between groups were tested by t-test for continuous variables and the Fisher exact test for categorical variables.

RESULTS

A total of 73 cases with an NIA-AA ABC A3 score were identified. Demographic and pathologic characteristics, including assessment of Aβ-42 deposits are presented in Table 1. The patients ranged in age from 53 to 97 years with mean ± SD of 75 ± 11; 51% were male, and 49% were female. The mean brain weight before fixation was 1159 ± 164 g. Nearly three-quarters had only AD pathology; mixed pathologies included diffuse Lewy body disease and AD in 20%, progressive supranuclear palsy and AD in 4%, and Parkinson disease and AD in 3%. No case on which we performed TDP-43 IHC had TDP-43-related disease. On ABC scoring, 95% had a B3 score, while 66% had a C3 score. Figure 1 gives a graphical visualization of the pathological characteristics of all 73 cases. Of the 73 cases, 63 (86%) showed Aβ-42 deposits in the cerebellar parenchyma.

Among all cases, parenchymal CAA was observed in 14 cases: solely in arterioles in 1, only in capillaries in 4, and in both arterioles and capillaries in 9. Meningeal CAA was observed in 33 cases and was scored as scant in 5, occasional in 20, and widespread in 8. PC loss (with or without associated Bergmann gliosis) was present in only 9 cases (5 were focal and 4 multifocal), acute hypoxic-ischemic neuronal changes were observed in 2 cases, and torpedo formations, proximal axon swellings in PCs (31), were observed in 1 case (Fig. 2). No neuritic plaques were observed.

Among the 63 Aβ-42-positive cases, the molecular layer was involved in 53 (84%) cases, the PC layer in 31 (49%) cases, and the granular cell layer in 22 (35%) cases. Of the 39 with granular cell layer involvement, 35 (90%) had molecular layer involvement. A diffuse morphology of Aβ-42 staining was observed in three-quarters of the cases (Fig. 3A); compact plaques in one-third (Fig. 3B); and cored plaques in 16%, all of which corresponded to dense amyloid plaques identified on H&E (Fig. 3C, D). More than one morphology was observed in 14 cases: 11 had both diffuse and compact, while 3 had both compact and cored morphologies (Fig. 3E, F). Most Aβ-42 deposits were widespread (41%) and intense (49%).

Among the 63 Aβ-42-positive cases, meningeal CAA (Fig. 3G) was observed in 30 (47%) cases: Aβ-42 staining in this compartment was scant in 4 (6%) cases, occasional circumferential staining was observed in 18 (29%) cases, and widespread circumferential staining was observed in 8 (13%) cases. Parenchymal CAA was observed in 11 (17%) cases, 8

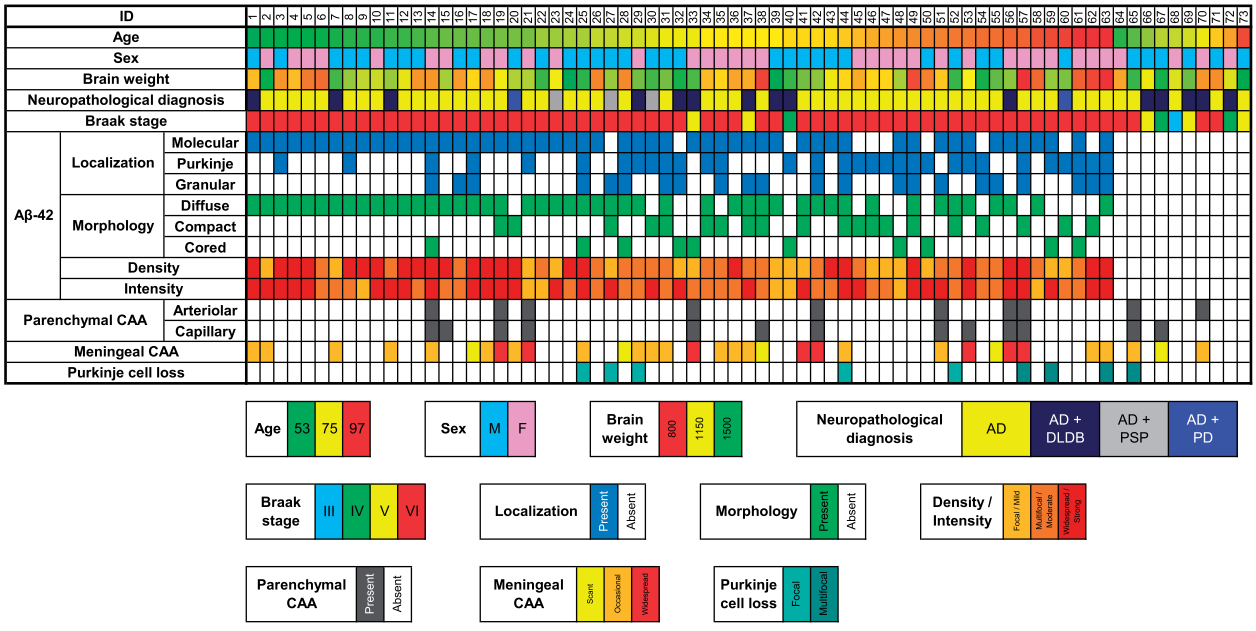

Figure 1. Heatmap-like visualization of the demographic and pathological data of the 73 cases included in this study. Parameters are color-coded according to the legend above. Parenchymal Aβ-42-positive cases are clustered on the left. AD, Alzheimer disease; CAA, cerebral amyloid angiopathy; DLBD, diffuse Lewy body disease; PD, Parkinson disease; PSP, progressive supranuclear palsy.

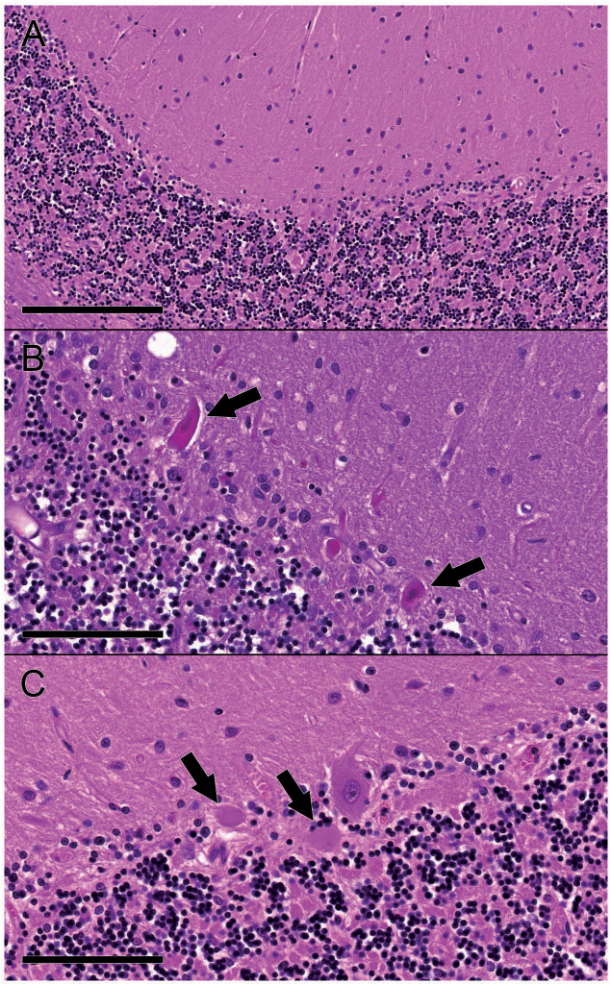

Figure 2. Neuropathological findings in the cerebellum of AD patients. A decrease in PC density was noted in a subset of cases (**A**, H&E). A single case showed focal hypoxic-ischemic changes in PCs with mild Bergmann gliosis (**B**, H&E). Occasional torpedo formations (arrows) were observed (**C**, H&E). AD, Alzheimer disease; H&E, hematoxylin and eosin; PC, Purkinje cell. Scale bars: **A** = 200 μm; **B**, **C** = 100 μm.

(13%) cases had both arteriolar and capillary positivity, and 3 (5%) cases had only capillary positivity (Fig. 3H). Additionally, 8 (13%) had morphological evidence of PC loss, which was focal in 5 (8%) cases and multifocal in 3 (5%). Torpedo formations were noted in 2 (3%) cases. Parenchymal CAA was associated with meningeal CAA (Table 2, $p < 0.01$). Table 3 summarizes the characteristics of Aβ-42 deposits between cases with PC loss and cases with a normal PC population. The only difference was that cases with Aβ-42-positivity in the PC layer had double the PC loss prevalence observed in cases without Aβ-42 staining in the PC layer (88% vs 44%, Table 3, $p = 0.03$).

Cases with cerebellar Aβ-42 positivity ($n = 63$) and those with cerebellar Aβ-42 negativity ($n = 10$) did not differ significantly in mean age (75 vs 75 years), mean brain weight (1152 vs 1205) or proportion male (49% vs 60%). Similarly, no differences in proportion of those with parenchymal CAA (17% vs 30%), meningeal CAA (46% vs 30%), or PC loss (13% vs 10%) were evident. Cases with cerebellar Aβ-42 deposition had a higher proportion with a B3 score (Braak stage V/VI) compared with cerebellar Aβ-42-negative cases (98% vs 70%, $p < 0.01$).

DISCUSSION

In this study, over 85% of autopsy cases with an A3 score according to the NIA-AA ABC criteria of AD had evidence of cerebellar parenchymal Aβ-42 deposition. The A3 cases with cerebellar parenchymal Aβ-42 deposition did not differ significantly from those without in sex, age, neuropathological diagnosis, C score, or PC loss. However, cases with parenchymal Aβ-42 deposition had a higher proportion of cases with a B3 score/Braak stage V-IV than Aβ-42-negative cases (98% vs 70%).

The diffuse morphology of Aβ-42 staining in the molecular layer was the most frequently observed pattern of positivity and was characterized by a wispy, polymorphic, fibrillary, and hazy deposition of Aβ-42 variably scattered throughout the thickness of the molecular layer (6, 32, 33). Unique to the cerebellum, within the molecular layer Aβ-42 positivity was consistently arranged in a linear manner perpendicular to the pial surface, which is suggestive of deposition along Bergmann glial fibers.

PC loss was associated with Aβ-42 positivity in the PC layer (Fig. 4), but no significant differences were observed in the intensity or density of Aβ-42 staining between cases with and without PC loss. PC loss in Aβ-negative cases may be due to cerebrovascular pathology (e.g. CAA) or other comorbidities. A decrease in PC density and dendritic arborization has been described in the cerebellum of AD patients (11, 34) and may be associated with both cognitive and motor dysfunction in these patients (15). The observation that Aβ-42 localization in the PC layer correlates with PC loss could be indirect evidence of a neurotoxic role of Aβ-42 for PCs. In fact, Aβ-42 has been shown to act deleteriously at both pre- and post-synaptic levels in PCs, possibly due to a pro-inflammatory mechanism (19). Our results, by linking PC loss to PC layer Aβ-42-positivity, highlight the potential role of Aβ-42 as a neurotoxic agent to PCs, in a pre-synaptic mechanism or pathway possibly linked to basket cell synapses to the PC soma (35); however, it is also possible that Aβ-42 is deposited locally after a PC degenerates. A previous study showed no association between Aβ-42 deposition and PC damage (20). Here, we illustrate the hypothesized damage indirectly by linking Aβ-42 deposition in the PC layer with PC loss. In addition, one case in our cohort had Aβ-42 PC layer deposition, PC loss, and torpedo formations, the latter directly indicating PC damage. Ultrastructural (12) and/or spatial proteomic (36) analyses may help elucidate the relationship between Aβ-42 deposition and PC damage.

Our study illustrates the seldom described cerebellar CAA characteristics in AD patients (37). Specifically, in our AD patients with an A3 NIAA-ABC score, nearly half (49%) of the 63 with cerebellar Aβ-42-positivity had CAA (1 with parenchymal CAA only, 20 with meningeal CAA only and 10 with both). Neither meningeal nor parenchymal CAA was

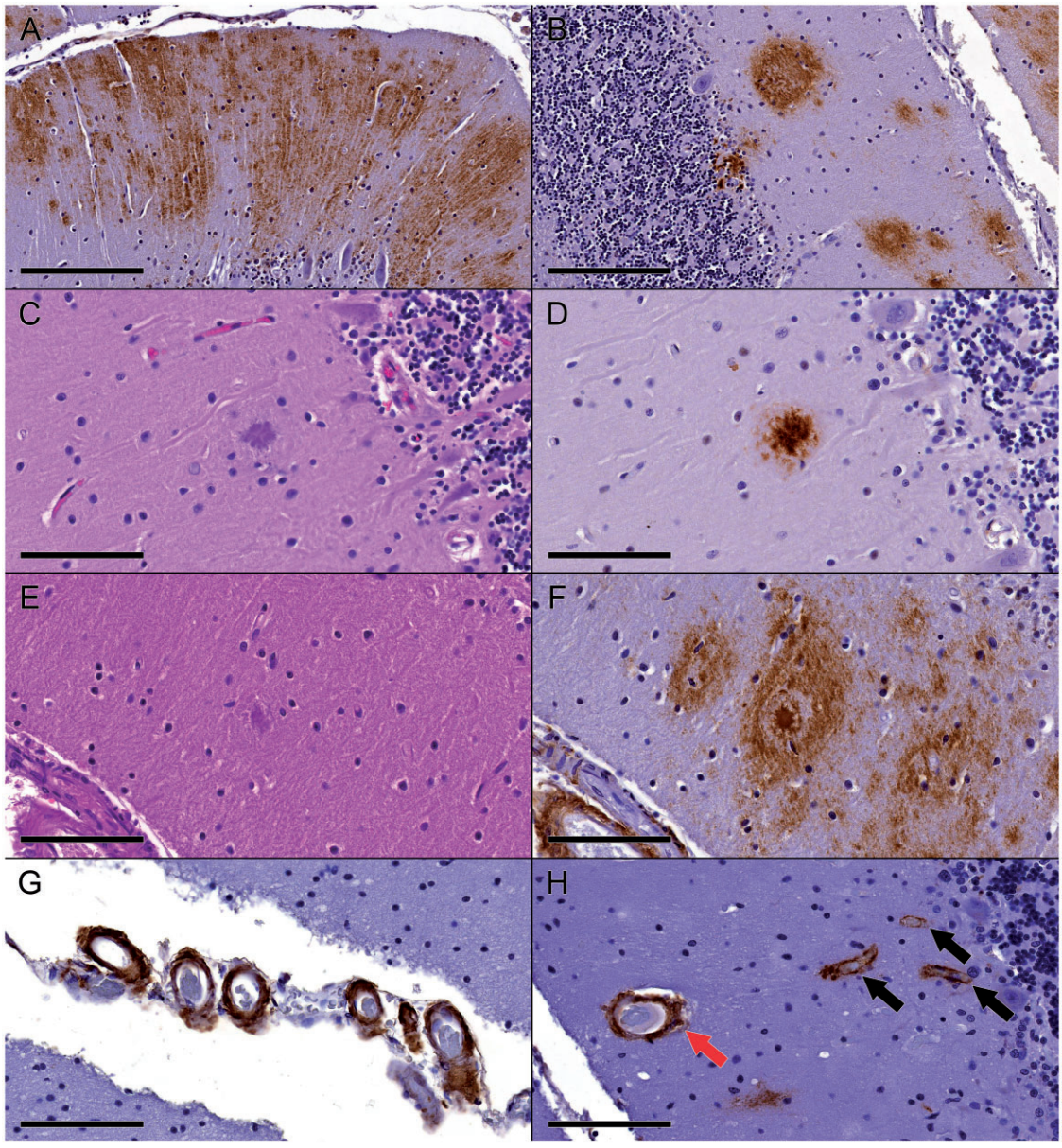

Figure 3. Aβ-42 staining morphology in the cerebellum of AD patients. A diffuse morphology was observed in the majority of cases, predominantly in the molecular layer (**A**, Aβ-42 IHC). A compact morphology was observed in many cases, in all layers (**B**, Aβ-42 IHC). Both diffuse and compact morphologies had no corresponding morphological correlate on H&E. Cored plaques stained intensely, either isolated (**C**, H&E; **D**, Aβ-42 IHC; same area) or with surrounding compact immunoreactivity (**E**, H&E; **F**, Aβ-42 IHC; same area). Meningeal CAA was highlighted by Aβ-42 staining (**G**, Aβ-42 IHC). Parenchymal CAA (**H**, Aβ-42 IHC) was observed in the arterioles (red arrow) and capillaries (black arrows). AD, Alzheimer disease; CAA, cerebral amyloid angiopathy; H&E, hematoxylin and eosin; IHC, immunohistochemistry. Scale bars: **A**, **B** = 200 μm; **C**-**H** = 100 μm.

Table 2. Association between parenchymal and meningeal CAA in cases with and without parenchymal A*β*-42 deposition in the cerebellum

		All cases (n = 73)		**Aβ-42 positive cases (n = 63)**		**Aβ-42 negative cases (n = 10)**	
				Parenchymal			
		CAA+ (%)*	**CAA− (%)**	**CAA+ (%)**	**CAA− (%)**	**CAA+ (%)**	**CAA− (%)**
Meningeal	CAA+ (%)	13 (18%)	20 (27%)	10 (16%)	20 (32%)	3 (30%)	0
	CAA − (%)	1 (1%)	39 (53%)	1 (2%)	32 (51%)	0	7 (70%)

All p values are >0.05, Fisher exact test. CAA, cerebral amyloid angiopathy.
* % of total.

Table 3. Aβ-42 characteristics among Aβ-42-positive cases with or without PC loss, and association between Aβ-42 staining in the PC layer and PC loss

Aβ-42 positive cases (n = 63)			**PC loss (%)**	**PC normal (%)**
N			8	55
Aβ-42	Localization, layer	Molecular	7 (88)	46 (84)
		Granular	5 (63)	17 (31)
		PC	7 (88)	24 (44)
		Non-PC	1 (13)	31 (56)
	Morphology	Diffuse	6 (75)	41 (75)
		Compact	4 (50)	16 (29)
		Cored	2 (25)	8 (15)
	Density	Focal	2 (25)	14 (26)
		Multifocal	2 (25)	19 (35)
		Widespread	4 (50)	22 (40)
	Intensity	Mild	0	7 (13)
		Moderate	2 (25)	23 (42)
		Strong	6 (75)	25 (46)

All p values are >0.05 except for comparison of PC loss between PC layer and non-PC layer positivity, where p = 0.03, Fisher exact test. PC, Purkinje cell.

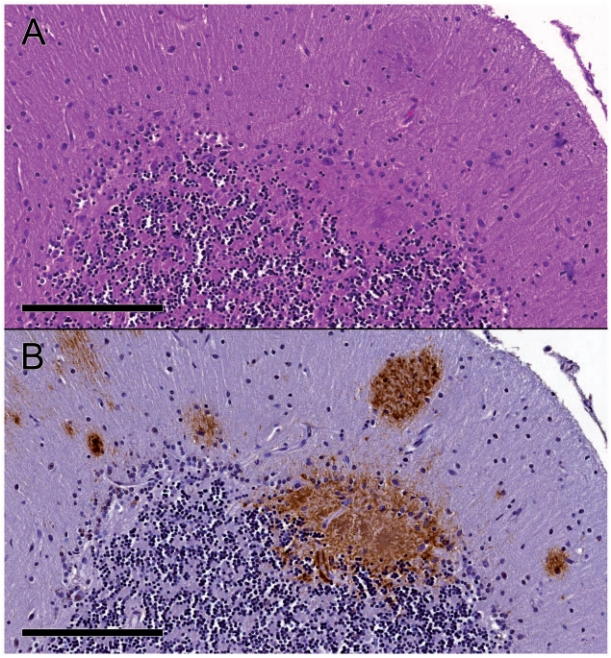

Figure 4. Aβ-42 staining in an AD case with PC loss (**A**, H&E). PC layer localization (**B**, Aβ-42 IHC) was observed in larger proportions of cases with PC loss compared with cases without PC loss. Aβ-42 staining densities and intensities were observed in similar proportions in the 2 groups. AD, Alzheimer disease; IHC, immunohistochemistry; H&E, hematoxylin and eosin; PC, Purkinje cell. Scale bars: **A**, **B** = 200 μm.

associated with cerebellar non-vascular Aβ-42 deposition. Among the 63 Aβ-42-positive cases, parenchymal CAA-positivity was associated with meningeal CAA-positivity. In the 10 Aβ-42-negative cases, all meningeal CAA-positive cases also had parenchymal CAA. Moreover, no association was found between CAA, either parenchymal or meningeal, and PC loss, both in Aβ-42-positive and Aβ-42-negative cases. In our sample, no cerebellar microinfarcts were observed, even in cases with severe CAA. This finding suggests that the cerebellar compartment could be more resistant to CAA-related microbleeds or microinfarcts than other central nervous system areas (38).

Limitations of the present study include the analysis of a single section of cerebellar cortex and dentate nucleus per case; however, because Aβ-42 deposition is widespread in late-stage AD, one section is likely to be representative. More extensive sampling to characterize regional differences of β-amyloid deposition within the cerebellum may be warranted in future studies. Moreover, although we focused on Aβ42, Aβ40 is the more predominant form deposited in arteries/arterioles in CAA, and future studies are needed to characterize parenchymal and vascular Aβ40 and Aβ42 deposits in the cerebellum. In addition, since TDP-43 IHC was only performed on cases with a suspicion of TDP-43-related disease, it is possible that we may have missed cases with TDP-43 pathology, given that it is now recognized that it is seen in a significant percentage of the oldest-old and AD patients (39). Future studies are warranted to assess TDP-43 pathology in our cohort.

In conclusion, the cerebellum shows a unique pattern of Aβ-42 deposition in comparison with other brain areas, possibly due to its unique anatomic architecture, increased clearance of APP, and/or late-stage involvement in AD pathogenesis. An association between Aβ-42 deposition in the cerebellum and higher B score/Braak stages was observed in our sample. The frequency of PC loss was similar between cases with and without parenchymal Aβ-42 staining but Aβ-42 staining in the PC layer was associated with PC loss. Although numbers are small, especially in the latter group, these findings merit further investigation.

CONFLICT OF INTEREST

The authors have no duality or conflicts of interest to declare.

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