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White matter hyper-intensity patterns in patients with amyloid angiopathy and cerebellum involvement

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Abstract

Background: Pathological changes in the cerebral white matter can be determined both in small vessel disease and in cerebral amyloid angiopathy. The pattern of involvement may be different depending on the etiology and severity of the process. Objective of the study: Determination and analysis of the pattern of cerebral white matter changes in patients with amyloid angiopathy and involvement of the cerebellum.
Material and methods: Patients with intracerebral hemorrhages who were examined by magnetic resonance imaging were prospectively analyzed. Patients were diagnosed with cerebral amyloid angiopathy (CAA) according to Boston criteria. Changes in white matter were interpreted using the Fazekas scale and compared for patients with CAA and patients with CAA and cerebellar involvement. Of the 614 patients with intracerebral hemorrhage, 96 were examined by cerebral magnetic resonance imaging. Of these, 41 patients were diagnosed with amyloid angiopathy, 19 patients with possible amyloid angiopathy, 21 patients – probable and 1 case with defined amyloid angiopathy.
Results: Cerebellar involvement was determined in 34% (14/41) of cases. Severe changes in white matter (Fazekas 2-3) were seen in patients with cerebellar involvement (12/14; 86% versus 8/27 and 30% p = 0.002).
Conclusions: Involvement of the white matter in the pathological process is more significant in patients with amyloid angiopathy and the involvement of the cerebellum, even after adjusting for risk factors. Patients with cerebellar haemorrhage and severe white matter should be screened for amyloid angiopathy.
Key words: amyloid, angiopathy, cerebral, white matter.

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Introduction

Cerebral amyloid angiopathy (CAA) is characterized by β-amyloid deposition in the media and adventitia of small and medium vessels of the cerebral cortex, subcortex, and leptomeninges [1-3]. CAA is a major cause of spontaneous lobar intracerebral hemorrhage (ICH) in normotensive elderly [1-3]. Hereditary and sporadic forms may occur, and the latter increases with age [2, 4-8]. ICH can take the form of macro-hematoma (MH) or micro-bleedings (MB) with various clinical presentations [9]. CAA frequently involves the occipital lobes, followed by the frontal, temporal, or parietal lobes, respectively [5, 9], but involvement of the cerebellum in CAA remains uncertain [5, 10]. Micro- or macro-hemorrhages in the deep brain structures or brainstem are an exclusion criterion for CAA.

The objectives of the current study were to assess the presence of cerebellar involvement in patients with CAA according to the modified Boston criteria [5] and to study the changes in the white matter.

Patients with spontaneous ICH were collected in two academic tertiary care centers and were included in a continuous database. The institutional IRB (Hadassah Medical Organization) approved the anonymous collection of data in this database and waived the need for informed consent.

For the current analysis, we retroactively analyzed the data accumulated in the period 2009-2015. The diagnosis of spontaneous ICH was confirmed in all patients using non-contrast computed tomography (CT). Patients with ICH secondary to trauma, vascular malformations, or tumors were excluded.

Material and methods

All 614 included patients underwent a standardized MRI protocol that included susceptibility weighted imaging or T2 star imaging (SWI or T2 * respectively) as soon as possible after the hemorrhage. Recommendations for performing post-ICH MRI were left to the discretion of participating neurologists and were based on clinical suspicion of CAA or atypical presentation or localization of the bleeding on CT. From the group of patients who had MRI, we identified patients who met the diagnostic criteria for CAA, according

to the modified Boston criteria [5]. Patients with non-lobar ICH and systolic blood pressure over 150 mmHg were considered to have a hypertensive ICH.

In patients who have undergone surgical procedures to remove the hematoma or decompressive craniectomy, the biopsy material has been studied for the presence of vascular amyloid deposits. Hematoma types, location and volumes were accumulated along with the vascular risk factor being noted. Bleedings were classified as MH or MB [5, 14] by experienced vascular neurologists and the absolute number of MB in the cerebral cortex were counted. The SWI or T2 * sequences were used to identify MB, while the other sequences were used to exclude MB mimicry, according to STRIVE criteria [15]. The presence of superficial cortical siderosis (CSS) has been documented and CSS has been classified as disseminated if it involved more than three grooves according to current recommendations [16-18]. Hyperintensities of deep white matter were measured on T2 FLAIR according to STRIVE methods [15] and according to the Fazekas scale [19] (0 – none, 1 – dotted scattered, 2 – starting to be confluent and 3 – confluent) and dichotomized in severe (grade 2-3) or non-severe (grade 1-2).

Patients with CAA and cerebellar involvement were compared to patients with CAA without any cerebellar involvement. Cerebellar MB locations were studied and divided into superficial cortical versus deep, involving the nuclei [11, 20].

Neurological deficit was analyzed using the National Institute of Health Stroke Scale (NIHSS) at admission and discharge. Disability was studied with the modified Rankin scale (mRS) at discharge and day 90 post-ICH.

Statistical analysis was performed using SPSS software. The Student's t-test was used to compare continuous variables and the chi-square test was used to compare nonparametric variables.

A multivariate regression analysis model was used to determine the factors that are associated with cerebellar involvement in patients with CAA. This model controlled for age, the severity of superficial siderosis, the existence of previous of ICH, the severity of the stroke at presentation, the volume of ICH, and the number of cortical micro-hemorrhages counted.

Results

Overall, 614 patients with spontaneous ICH were included in our database (343 at one center and 241 at the other) and 85 (54 and 31, respectively) had a post-ICH MRI (14%). Of the 85 patients, 41 (48%) were diagnosed with CAA according to the modified Boston criteria [5] (19 possible CAAs, 21 probable CAAs, and 1 defined CAA).

MRI patients were significantly younger (67.3 ± 12.2 versus 72.4 ± 12.9; p = 0.005) and had significantly lower hemorrhage volumes (13.2 ± 20.9 vs. 36 .0 ± 57.2 cc; p = 0.003) compared to non-NMR group. Hypertension was significantly more common in patients who did not have MRI (67% versus 13%; p = 0.034), but other risk factors did not differ between groups.

In the total group of 614 patients, 64 (10%) presented with cerebellar MH, and 10 of them had MRI. Most of the 54 patients who presented with cerebellar MH who did not have an MRI (95% and 72% of the patients in the participating centers) had hypertensive ICH.

In the CAA-related hemorrhage group, cerebellar participation was present in 34% (14 of 41 patients). Most cerebellar lesions were MB (fig. 1) and most patients had multiple cerebellar lesions (mean 8.4 ± 13.3). Cerebellar MB was more frequently superficial (11/14 patients involved superficial cerebellar, 2/14 had deep cerebral MB and 1/14 combined deep and superficial MB). A more severe degree of white matter hyperintensity (Fazekas 2–3) was more common in patients with cerebellar involvement (12/14; 86% vs. 8/27; 30% p = 0.002).

Clinical variables including age, sex, risk factor profile, stroke severity, 90-day mRS scores, or survival were not different between CAA patients with and without cerebellar involvement (tab. 1).

Patients with CAA-related cerebellar involvement had a significantly higher number of lobular cortical MB compared

Table 1

Baseline characteristics of patients with CAA

	CAA without cerebellar hemorrhage (n = 27)	CAA with cerebellar hemorrhage (n = 14)	P value
Age (mean ± SD)	70.5 ± 9.4	69.8 ± 8.2	0.82
Gender male (%)	13 (48%)	7 (50%)	0.910
Hypertension (%)	14 (52%)	8 (57%)	0.747
Diabetes (%)	3 (11%)	4 (29%)	0.159
Previous stroke (%)	3 (11%)	4 (29%)	0.159
Previous ICH (%)	3 (11%)	3 (21%)	0.375
Smoking (%)	3 (11%)	2 (14%)	0.768
Family history of ICH (%)	0 (0)	1 (7%)	0.160
Vitamin K antagonists (%)	2 (7%)	2 (14%)	0.482
Antiplatelet (%)	10 (37%)	8 (57%)	0.219
NOACs (%)	0 (0)	1 (7%)	0.457
History of dementia (%)	1 (7%)	3 (21%)	0.070
Hematoma size (ml mean ± SD)	26 ± 29.5	17.3 ± 21.1	0.315
Ventricular extension (%)	1 (7)	0 (0)	0.457
Spot sign (%)	1 (7)	0 (0)	0.248
Admission NIHSS (mean ± SD)	5.4 ± 5.5	4.0 ± 4.0	0.418
Total cortical microbleeds (mean ± SD)	2.8 ± 8.5	37.9 ± 39.6	< 0.00001
Confluent white matter hyperintensities (%)	8 (30)	12 (86)	0.002
Disseminated cortical superficial siderosis (%)	1 (3.7)	3 (21.4)	0.107
Modified Rankin score≤2 at day 90 (%)	13 (48)	6 (43)	0.747
Mortality (%)	2 (7)	0 (0)	0.296

ICH – Intracerebral hemorrhage, NOAC – Non-Vitamin K oral anticoagulants, NIHSS – National Institute of Health Stroke Scale. *Fazekas score 2–3.

to patients without cerebellar involvement (37.8 ± 39.5 vs. 2.8 ± 8.5; p <0.00001). CSS was present in 11 patients who had MRI and was classified as disseminated in 3. However, the absolute combined number of macro-hemorrhages (old + new) or the presence of disseminated CSS (> 3 grooves) did not differ significantly (7.3 vs. 2.4%; p = 0.07).

In the multivariate analysis that controls age, stroke severity, previous ICH episodes, number of micro-bleeds, age, and severity of superficial siderosis, the only variable that was significantly correlated with cerebellar involvement in CAA patients was the number of cortical hemorrhages (OR 1.045, 95% CI 1.005-11.087) (tab. 2). Interestingly, the severity of stroke was inversely correlated with cerebellar involvement in patients with CAA (OR 0.814 95% CI 0.664–0.997).

Table 2

Multivariate analysis for cerebellar CAA presence

Variable	OR	P	95% C.I.
Age (yr)	1.018	0.604	0.952 - 1.089
Previous ICH	1.729	0.564	0.269 - 11.135
Hematoma size (ml)	1.016	0.353	0.982 - 1.051
Degree of superficial siderosis	1.518	0.052	0.997 - 2.311
Number of MB	1.045	0.025	1.005 - 1.087
Admission NIHSS	0.814	0.047	0.664 - 0.997

ICH – intracerebral hemorrhage, MB – micro bleeds,
NIHSS – National Institute of Health Stroke Scale.

Discussion

The current study shows that cerebellar involvement is not uncommon in CAA-related ICH. Most patients have multiple cerebellar MBs, but some have only had MH involving the cerebellum in combination with MB in the cerebral cortex. Clinical features do not differ between CAA patients with or without cerebellar involvement, but patients with cerebellar involvement have a higher number of MB cortical lobar and also more often tend to have more intensity of white matter hyper-intensity, measured with the Fazekas score.

In both patients with CAA and patients with small vessel disease (SVD), white matter hyperintensities (WHM) are seen, but the patterns of subcortical WMH are different. In our study age did not prove to be associated with the severity of white matter involvement, or with the number of microbleeds seen in the cerebellum. However, the finding that WMH are more severe in patients with cerebellar involvement may be used a marker of CAA-related leukoaraiosis or of cerebrovascular amyloid load.

Our findings show that cerebellar involvement was observed in 43% of patients diagnosed with CAA based on the modified Boston criteria [5]. Both MB and MH were observed in our patients, most of the bleeding being of the MB type. Also, most patients with cerebellar involvement appear to have numerous lobar MBs (mean value of 37.8 ± 39.5) and a more severe degree of white matter hyper-intensities, which may involve a more severe or prolonged course of the disease.

The presence and number of lobar MBs as well as white matter burden have been associated with cognitive decline in patients with CAA [23]. Cognitive testing was not typically performed upon admission to our data sets, and therefore we cannot confirm this application. However, mRS scores at 90 days or survival do not differ between those with or without cerebellar involvement.

It should be noted that previous studies examining the pathological and radiological findings of CAA, as well as small vessels disease, have not examined the involvement of cerebellums [14, 16, 23, 24]. Brain MBs are divided into MBs in the lobar, which are largely secondary to CAA, and deep MBs, which are largely secondary to hypertension [3, 14, 23-25]. Because the cerebellum is a relatively common site for hypertensive ICH, it could be speculated that cerebellar MB, together with WMH, may also be linked to chronic hypertension [11]. However, in the light of findings of the current study, cerebellar MB may be correlated with the advance of CAA, could support the hypothesis that WMH in CAA has a distinct pattern that may be a marker of amyloid load and be included in the future diagnostic criteria for CAA.

For unknown reasons, CAA tends to involve the posterior lobes areas that are provided by the posterior circulation. Because the cerebellum is also provided by posterior circulation, similar mechanisms that are currently unknown may also be responsible for the involvement of the cerebellum in CAA.

Our study has significant limitations. First, although the study was based on potentially accumulated data, not all patients with ICH underwent MRI and the decision to perform or not MRI was left to the discretion of the neurologist who might be prejudiced. However, the indications and rate for MRI were similar between centers, as were all other patients' characteristics. Although this can only reflect national preferences, in reality it reflects daily practices in academic centers where not all patients with ICH, especially those with suspected hypertensive ICH, are subjected to magnetic imaging.

Second, the diagnosis of CAA according to the modified Boston criteria is based on the presence of MRI markers. These criteria have high specificity, but lower sensitivity, because CAA can be underdiagnosed in cases where MRI is not performed. Third, as a registry-based cohort study, variations in data acquisition over time or between centers are possible. Finally, long-term cognitive data as well as data on ICH recurrence rates were not available and could have added value to our study, given that cerebellar involvement was more common in patients with a greater number of cortical MB.

Conclusions

Our data shows that cerebellar involvement may be quite common in patients with CAA, especially when CAA has been more advanced, as noted by the association with higher numbers of lobar CMB, CSS, and more severe white matter hyper-intensities. Cerebellar involvement may be present as cerebellar MH or more frequently as cerebellar MB in patients with lobar MH, and tends to be

more frequently superficial, i.e. not involving the cerebellar nuclei, and more often associated with a more severe form of white matter abnormality. Clinical presentation of patients with cerebellar involvement in CAA and without cerebellar involvement does not appear to differ. Severe white matter changes seen on non-contrast CT in patients with lobar or cerebellar hemorrhage should prompt the treating physician to perform MRI and to look for CAA.

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Authors' contribution
PG and RL researched literature and conceived the study. RL wrote the first draft of the manuscript. MG and SG revised and approved the manuscript. All the authors were involved in protocol development, patients' recruitment, and data analysis, reviewed, edited and approved the final version of the manuscript.

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The ethics committee of Hadassah-Hebrew Univerity Medica center approved this study and waived the need for obtaining informed consent. Guarantor: RL.

Conflict of Interests
All the authors declare that there is no conflict of interests.