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Cerebellar hemorrhages in patients with cerebral amyloid angiopathy

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ABSTRACT

Background: Cerebral amyloid angiopathy (CAA) typically involves the cerebral cortex but whether it affects the cerebellum remains uncertain.
Methods: Patients with intracerebral hemorrhage (ICH) who underwent magnetic resonance imaging were prospectively enrolled. Patients were diagnosed with CAA according to the Boston criteria and their hemorrhage types were categorized as macro-hematoma (MH) or microbleeds (MB). Patients with CAA and cerebellar involvement were compared with CAA patients without cerebellar involvement.
Results: Out of 614 patients with ICH, 85 (14%) had a post-ICH MRI. Of those, 41 (48%) were diagnosed with possible (n = 19), probable (n = 21) or definite (n = 1) CAA. Cerebellar involvement was seen in 14/41 (34%) patients with CAA. Most cerebellar lesions were of the MB type (35%) and most patients had several cerebellar MB typically involving the cerebellar cortex (85%). Patients with cerebellar involvement had larger numbers of lobar MB but clinical variables including age, gender, risk factor profile, mRS scores at 90 days or survival did not differ between those with and without cerebellar involvement.
Conclusions: Cerebellar involvement may be common in CAA. Most patients have multiple superficial cerebellar MB. Clinical characteristics do not differ between CAA patients with or without cerebellar involvement. Patients presenting with cerebellar ICH should be screened for CAA with MRI.

1. Introduction

Cerebral amyloid angiopathy (CAA) is characterized by deposition of β-amyloid in the media and adventitia of small and medium-sized vessels of the cerebral cortex, sub-cortex, and leptomeninges [1–3]. CAA is an important cause of spontaneous lobar intracerebral hemorrhage (ICH) in normotensive elderly [1–3]. Hereditary and sporadic forms may occur and the latter increases in both prevalence and severity with age [2,4–8]. ICH may take the form of macro-hematoma (MH) or micro bleeds (MB) with varying clinical presentations [9]. CAA frequently involves the occipital lobes, followed by the frontal, temporal or parietal lobes respectively [5,9]. Involvement of the deep cerebral structures or brain stem represent exclusion criteria for CAA related ICH [5]. Involvement of the cerebellar hemisphere in CAA remains uncertain [5,10] although a recent study suggested that superficial cerebellar involvement can be seen in CAA [11]. The goals of the current study were to evaluate the presence of cerebellar involvement in patients with CAA according to the modified Boston criteria [5] and to study the attributes of such involvement.

2. Patients and methods

All patients with spontaneous ICH admitted to two tertiary care academic centers were included in an ongoing database as previously described [12]. The institutional IRB (Hadassah Medical Organization) approved anonymous collection of data into this database and waived the need for informed consent. For the current analysis we retrospectively analyzed data accrued during 2009–2015. Diagnosis of spontaneous ICH was confirmed in all patients using a non-contrast computerized tomography scan (CT) and some patients also underwent CT angiography as part of our standard protocol for detecting the spot sign [13]. Contrast was withheld in patients with known allergies to

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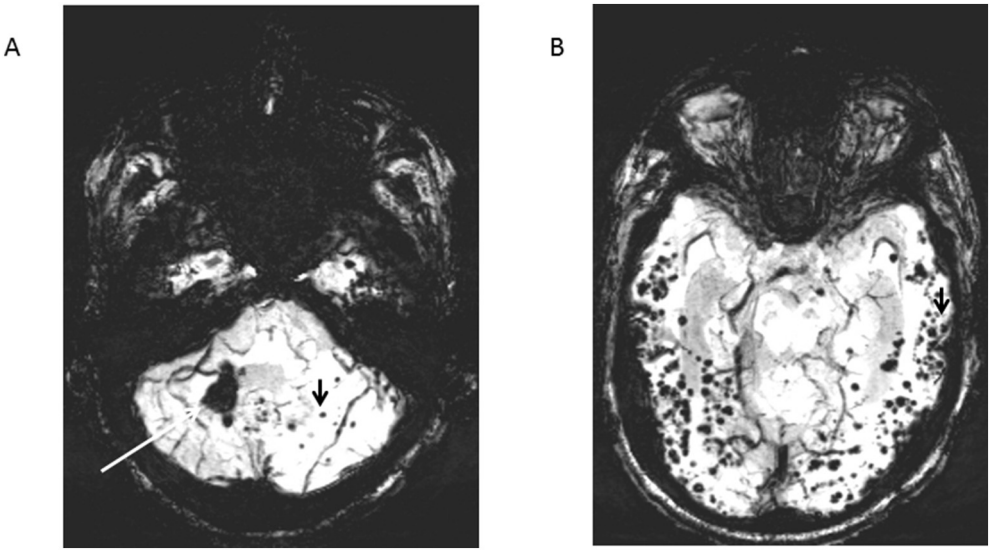

Fig. 1. Typical SWI MRI images from a patient with hypo-intense cerebellar macro (A. long white arrow) and micro-hemorrhages (short black arrow) as well as cortical lobar micro-hemorrhages (B, short black arrow) typical for cerebral amyloid angiopathy.

iodine and in those with abnormal kidney functions. Patients with spontaneous ICH who also underwent magnetic resonance imaging (MRI) were specifically included in the current study. Patients with ICH secondary to trauma, vascular malformations or tumors were excluded.

All included patients underwent a standardized MRI protocol that included susceptibility weighted or T2 star imaging (SWI or T2* respectively) as soon as possible after the ictus. Recommendations to perform post-ICH MRI were left to the attending neurologists' discretion and were based on clinical suspicion for CAA or on atypical presentation or location of the hemorrhage on CT. From the cohort of patients that had an MRI we identified patients fulfilling diagnostic criteria for CAA according to the modified Boston criteria [5]. Patients presenting with non-lobar ICH and systolic blood pressure over 150 were considered to have a hypertensive ICH. Furthermore, patients with both deep and cortical bleeds were considered to have non-CAA ICH. In patients that underwent surgical procedures for hematoma evacuation or decompressive craniectomy, biopsy material was studied for the presence of vascular amyloid depositions. Hematoma types, location and volumes were accrued along with vascular risk factor profile. Hemorrhage types were categorized as MH or MB [5,14] by experienced vascular neurologists and the absolute MB numbers in the cerebral cortex were counted. MB were identified on SWI or T2* sequences, and other sequences were used to rule out MB mimics, according to the STRIVE criteria [15]. Cortical superficial siderosis (CSS) presence was documented and CSS was graded as disseminated if it involved more than three sulci according to current recommendations [16–18]. Deep white matter hyperintesities were measured on T2 FLAIR according to STRIVE methods [15] and by the Fazekas scale [19] (o – none, 1 – punctate scattered, 2 - beginning to be confluent and 3 - confluent) and dichotomized into severe (grade 2–3) or non-severe (grade 1–2).

Patients with CAA and cerebellar involvement were further compared with CAA patients with no cerebellar involvement. Locations of cerebellar MB was studied and divided into superficial cortical vs. deep cerebellar involving the nuclei, as described recently [11,20].

Neurological severity was studied with the National Institutes of Health Stroke Scale (NIHSS) on admission and at discharge. Disability was studied with the modified Rankin Scale (mRS) at discharge and day 90 post ICH.

Statistical analysis was performed with the SPSS software. Student's *t*-test was used for comparison of continuous variables and the χ-square test was used for comparison of nonparametric variables. We then used a multivariate regression analysis model to determine factors that are associated with cerebellar involvement in patients with CAA. This model controlled for age, severity of superficial siderosis, existence of prior ICH episodes, stroke severity on presentation, volume of the ICH leading to presentation, and the number of cortical micro-bleeds observed.

3. Results

A total of 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 those 85 patients, 41 (48%) were diagnosed with CAA according to the modified Boston criteria [5] (19 possible CAA, 21 probable CAA and 1 definite CAA).

Patients that had an MRI were significantly younger (67.3 ± 12.2 vs. 72.4 ± 12.9; p = .005) and had significantly smaller hemorrhage volumes (13.2 ± 20.9 vs. 36.0 ± 57.2 cc; p = .003) compared with the non-MRI group. Hypertension was significantly more prevalent in patients that did not have MRI (67% vs. 13%; p = .034) but other risk factors did not differ between the groups.

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

In the CAA- related hemorrhage group cerebellar involvement was present in 34% (14 of 41 patients). Most cerebellar lesions were MB (Fig. 1) and most patients had several cerebellar lesions (mean 8.4 ± 13.3). Cerebellar MB were more frequently superficial (11/14 patients had superficial cerebellar involvement, 2/14 had deep cerebellar MB and 1/14 had combined deep and superficial MB). A more severe white matter hyperintensities grade (Fazekas 2–3) was more frequent in patients with cerebellar involvement (12/14; 86% vs. 8/27; 30% p = .002).

Clinical variables including age, gender, risk factor profile, stroke severity, mRS scores at 90 days, or survival did not differ between CAA patients with and without cerebellar involvement (Table 1).

Patients with CAA related cerebellar involvement had significantly larger numbers of lobar cortical MB when compared to patients without cerebellar involvement (37.8 ± 39.5 vs. 2.8 ± 8.5; p < .00001). CSS was present in 11 patients that had an MRI and was categorized as disseminated in 3. However, the combined absolute number of macro-hemorrhages (old + new) or the presence of disseminated CSS (> 3 sulci) did not differ significantly (7.3 vs. 2.4%; p = .07).

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[a] (%)	8 (30)	12 (86)	0.002
Disseminated cortical superficial siderosis (%)	1 (3.7)	3 (21.4)	0.107
Modified Rankin socre ≤ 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 Institutes of Health Stroke Scale.
[a] Fazekas score 2–3.

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 Institutes of Health Stroke Scale.

On multivariate analysis controlling for age, stroke severity, existence of prior episodes of ICH, number of micro-bleeds, age and the severity of superficial siderosis, the only variable that was significantly correlated with cerebellar involvement in patients with CAA was the number of cortical micro-bleeds (OR 1.045, 95% CI 1.005–1.087) (Table 2). Interestingly, stroke severity was inversely correlated with cerebellar involvement in patients with CAA (OR 0.814 95% CI 0.664–0.997).

4. Discussion

The current study shows that cerebellar involvement in not rare in CAA-related ICH. Most patients have multiple cerebellar MB but some only had MH involving the cerebellum in combination with MB in the cerebral cortex. Clinical characteristics do not differ between CAA patients with or without cerebellar involvement but patients with cerebellar involvement have larger numbers of cortical lobar MB and also more often tend to have more confluent white matter hyper-intensities as measured with the Fazekas score. In line with a recent publication [11], MB location in the patients with cerebellar CAA involvement was more frequently superficial suggesting more common accumulation of amyloid in the cerebellar cortical areas similar to the observation in cortical CAA.

Previous studies reported conflicting results concerning cerebellar involvement in patients with CAA [4,5,10,21]. Most patients with cerebellar MH included in our cohort had hypertensive ICH. Furthermore, most patients with cerebellar CAA only had cerebellar MB but in 3 patients (7%) a cerebellar MH led to the identification of cortical MB and/or CSS confirming a diagnosis of probable CAA. Although these cases represent a small portion of cerebellar ICH, they emphasize the importance of conducting magnetic imaging in patients with cerebellar MH especially in the absence of hypertension. Since many of these patients also have common cerebrovascular risk factors such as diabetes and hyperlipidemia, the identification of CAA in these patients may influence the selection of future medical treatments, especially anticoagulation, as the latter are generally contraindicated in patients with CAA [22]. The importance of CAA identification in these patients is also supported by Seifgge et al., who described increased prevalence of cerebellar MH, comparing ICH location among anticoagulated versus non-anticoagulated patients [21].

In addition, our findings indicate that cerebellar involvement was seen in 43% of patients diagnosed with CAA based on the modified Boston criteria [5]. Both MB and MH were seen in our patients, with most of bleeds being of the MB type. Also, most patients with cerebellar involvement appear to have numerous lobar MB, (mean value of 37.8 ± 39.5) and a more severe degree of white matter hyperintensities which may imply a more severe or a more prolonged disease course in these patients. The presence and number of lobar MB has been associated with cognitive decline in patients with CAA [23]. Unfortunately, cognitive testing was not performed routinely on admission in our datasets and therefore we cannot confirm this postulation. However, mRS scores at 90 days, or survival did not differ between those with or without cerebellar involvement.

For yet unknown reasons, CAA tends to involve the posterior lobar areas that are supplied by the posterior circulation. As the cerebellum is also supplied by the posterior circulation, it is possible that similar currently unknown mechanisms are also responsible for the cerebellar involvement in CAA.

It should be noted that most previous studies examining pathological and radiological findings of CAA in particular, and cerebral small vessel disease in general, did not examine cerebellar involvement [14,16,23,24]. Cerebral MB are commonly divided into lobar MB which are mostly secondary to CAA, and deep MB which are mostly secondary to hypertension [3,14,23–25]. As the cerebellum is a relatively frequent location for hypertensive ICH, one could speculate that cerebellar MB may also be related to hypertension. This was indeed reported previously by De Rouck and colleagues [10] who found that most of the cerebellar MB in a cohort of 9 patients with CAA were secondary to hypertension. However, the findings of the current study, which

showed that cerebellar MB may be correlated with advanced CAA, could support CAA as a possible cause for cerebellar MB. In line with the current results, a recent study reported a tendency for superficial cerebellar involvement in CAA related ICH [11]. In contrast, most hypertensive cerebellar ICH involved the deeper cerebellar nuclei [11].

Our study has significant limitations. First, although the study was based on prospectively accrued data, not all patients with ICH underwent MRI and the decision of whether or not to perform MRI was left to the attending neurologist discretion which may have introduced biases. However, the indications and rate for MRI were similar across centers as were all other patient characteristics. While this may merely reflect national preferences it does reflect daily practice in academic centers where not all patients with ICH, especially those with presumed hypertensive ICH, undergo magnetic imaging. Second, CAA diagnosis according to the modified Boston criteria is based on the presence of MRI markers. These criteria have high specificity but lower sensitivity, as CAA may be underdiagnosed in cases where MRI is not preformed or if no MRI markers are demonstrated yet. Third, as a registry-based cohort study, variations of 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 in light of the finding that cerebellar involvement was more frequent in patients with larger numbers of cortical MB.

In conclusion, our data shows that cerebellar involvement may be rather common in patients with CAA, especially when CAA was more advanced, as illustrated by the association with higher lobar CMBs counts and CSS. Cerebellar involvement may present as cerebellar MH or more commonly as cerebellar MB in patients presenting with lobar MH. Cerebellar MB in patients with CAA tend to more frequently be superficial-cortical and are more often associated with a more severe form of white matter abnormality. Patients with cerebellar involvement in CAA cannot be distinguished based on clinical grounds and cerebellar involvement does not seem to alter the short term outcome of patients with CAA although it is associated with a larger number of lobar MB which may imply a more severe or protracted form of CAA. Finally, why only a subset of patients have cerebellar involvement remains unknown and should be further studied.

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Ethical approval and informed consent

The ethics committee of HMO approved this study and waived the need for obtaining informed consent.

Guarantor: RRL.

Contributorship

RRL and PG researched literature and conceived the study. PG, JM, NEY, EU, AH, JMG and JEC were involved in protocol development, patient recruitment and data analysis. RRL wrote the first draft of the manuscript. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

Declaration of Competing Interest

All authors declare that there is no conflict of interest.

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