SUPPLEMENTAL MATERIALS

Cerebellar hematoma location: implications for the underlying microangiopathy

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Total number of Supplemental Tables: 3

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Supplemental methods

Patients selection

We performed a retrospective analysis of data drawn from an ongoing prospective cohort study

of ICH performed at Massachusetts General Hospital (Boston, MA, USA).[1,2] Study subjects were

consecutive spontaneous cerebellar ICH patients admitted to the Massachusetts General Hospital

between January 1, 1998, and January 1, 2016, with primary ICH. The term spontaneous cerebellar ICH

is defined as a non-traumatic hemorrhage in the cerebellar parenchyma, not secondarily caused by a

tumour, vascular malformation or aneurysm. In all patients, secondary causes of cerebellar-ICH were

ruled out by means of an extensive diagnostic work up (CT angiography in 72, MR angiography in 19 and

all the remaining 8 patients underwent an MRI with gadolinium injections) as previously described.[1,2]

Eighteen cerebellar ICH patients were excluded because the primary cerebellar bleeding could not be

reliably assessed on the admission CT for the following reasons: a) 4 patients because the CT scan was

not available, b) 10 patients because only a CT scan after surgery was available, 3) 3 patients because

they showed ≥ 2 simultaneous acute ICH at time of enrollment, 4) 1 patient had a posterior fossa cyst.

Furthermore, 38 cerebellar-ICH patients were excluded because the primary hematoma involved both

superficial and deep areas. Compared to enrolled patients, excluded patients had higher ICH volume,

more often underwent hematoma evacuation, and had increased 30-day mortality **(Supplemental Table**

I).

Baseline clinical data collection

Baseline data collection was performed as described previously.[3,4] Briefly, the following clinical

variables were systematically recorded for each participant: age, sex, hypertension, diabetes,

hypercholesterolemia, atrial fibrillation, history of ICH, history of ischemic stroke, pre-ICH treatment with warfarin, antiplatelets, or statins, and whether there was surgical hematoma evacuation.

CT scan data

All admission CT scans were evaluated and primary hematoma location was rated in the cerebellum. According to the hematoma location patients were divided in a) deep cerebellar-ICH (with and without peduncular involvement, **Figure 2, Panel A-B**); b) superficial cerebellar-ICH (with and without vermian involvement, **Figure 2, Panel C-D**); For definitions see also **Supplemental Table II** and **Supplemental Figure I**. In order to define the classification for the rating of the cerebellar hematoma location, raters (MP, SM, AM, AC, LX) established consensus criteria based on previous pathologic literature.[3,4] All disagreements in ratings between reviewers were resolved by consensus. Cerebellar hematoma location was rated blinded to all clinical and MRI information. Interrater agreement of the categorization of hematoma location was excellent (Cohen's kappa: 0.86).

MRI data

Images were obtained using a 1.5 Tesla MR scanner (GE Sigma) and included whole brain T2-weighted, T1 weighted, diffusion weighted images (DWI), T2*-weighted gradient-recalled echo and fluid attenuated inversion recovery (FLAIR). In seven cases, the blood-sensitive sequence used was Susceptibility Weighted Imaging (SWI). Neuroimaging markers of SVD severity were rated according to STRIVE consensus criteria.[5] CMB were defined on axial blood-sensitive MRI as punctate foci of hypointensity less than 10 mm in diameter, distinct from vascular flow voids and leptomeningeal hemosiderosis. Their presence and number were evaluated according to current consensus criteria and categorized according to the previously validated Microbleed Anatomical Rating Scale.[6,7] Based on location, CMB were categorized as stricly lobar-CMB, stricly deep-CMB and mixed-CMB.[8] Intrarater

agreement (MP) for presence of lobar, deep or Mixed-CMB was high (Cohen k=0.84). White matter

hyperintensities (WMH) were evaluated in axial brain FLAIR sequences using the Fazekas scale (range 0-

3).[9,10] We dichotomized patients into those with no/mild periventricular or deep WMH (score 0–1) and

those with moderate to severe periventricular or deep WMH (score 2–3). Global brain atrophy (GBA)

was rated according to axial brain T1-weighted imaging according to a previously validated 0–3 scale,

where 3 represents severe atrophy.[11] We dichotomized patients into those with no or mild atrophy (0–

1) and those with moderate to severe atrophy (2–3). Lacunes were defined as small, ovoid, subcortical

cavity of between 3 and 15 mm in diameter and hypointense on T1 imaging with corresponding

hyperintense lesion on FLAIR images.[1,5] Enlarged perivascular spaces (EPVS) were rated on axial T2-

weighted MR images, in the basal ganglia and centrum semiovale. We pre-specified a dichotomized

classification of EPVS degree as high (score >20) or low (score ≤20) in line with previous studies.[2,12] The

presence or absence of cortical superficial siderosis (cSS) was evaluated in this study, according to

current consensus criteria.[13]

All MRI analyses were performed and recorded blinded to all clinical information.

Supplemental statistical methods:

For dichotomous variables, the Fisher Exact Test was used for all comparisons. We did not correct for

multiple comparisons because our study was exploratory and hypothesis-generating.

Supplemental references:

1. Pasi M, Boulouis G, Fotiadis P, Auriel E, Charidimou A, Haley K, et al. Distribution of lacunes in cerebral amyloid angiopathy and hypertensive small vessel disease. *Neurology*. 2017;88:2162-2168

2. Charidimou A, Boulouis G, Pasi M, Auriel E, Etten ES van, Haley K, et al. MRI-visible perivascular spaces in cerebral amyloid angiopathy and hypertensive arteriopathy. *Neurology*. 2017;88:1157–1164.

3. Dinsdale HB. Spontaneous hemorrhage in the posterior fossa: a study of primary cerebellar and pontine hemorrhages with observations on their pathogenesis. *Arch. Neurol.* 1964;10:200–217.

4. Itoh Y, Yamada M, Hayakawa M, Otomo E, Miyatake T. Cerebral amyloid angiopathy: a significant cause of cerebellar as well as lobar cerebral hemorrhage in the elderly. *J. Neurol. Sci.* 1993;116:135–141.

5. Wardlaw JM, Smith EE, Biessels GJ, Cordonnier C, Fazekas F, Frayne R, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol.* 2013;12:822–838.

6. Greenberg SM, Vernooij MW, Cordonnier C, Viswanathan A, Salman RA-S, Warach S, et al. Cerebral microbleeds: a guide to detection and interpretation. *Lancet Neurol.* 2009;8:165–174.

7. Gregoire SM, Chaudhary UJ, Brown MM, Yousry TA, Kallis C, Jäger HR, et al. The Microbleed Anatomical Rating Scale (MARS) Reliability of a tool to map brain microbleeds. *Neurology*. 2009;73:1759–1766.

8. Caunca MR, Brutto VD, Gardener H, Shah N, Dequatre-Ponchelle N, Cheung YK, et al. Cerebral Microbleeds, Vascular Risk Factors, and Magnetic Resonance Imaging Markers: The Northern Manhattan Study. *J. Am. Heart Assoc.* 2016;5:e003477.

9. Fazekas F, Chawluk JB, Alavi A, Hurtig HI, Zimmerman RA. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. *Am. J. Roentgenol.* 1987;149:351–356.

10. Kapeller P, Barber R, Vermeulen RJ, Ader H, Scheltens P, Freidl W, et al. Visual Rating of Age-Related White Matter Changes on Magnetic Resonance Imaging: Scale Comparison, Interrater Agreement, and Correlations With Quantitative Measurements. *Stroke*. 2003;34:441–445.

11. Pasquier F, Leys D, Weerts JGE, Mounier-Vehier F, Barkhof F, Scheltens P. Inter-and Intraobserver Reproducibility of Cerebral Atrophy Assessment on MRI Scans with Hemispheric Infarcts. *Eur. Neurol.* 1996;36:268–272.

12. Martinez-Ramirez S, Pontes-Neto OM, Dumas AP, Auriel E, Halpin A, Quimby M, et al. Topography of dilated perivascular spaces in subjects from a memory clinic cohort. *Neurology*. 2013;80:1551–1556.

13. Charidimou A, Linn J, Vernooij MW, Opherk C, Akoudad S, Baron J-C, et al. Cortical superficial siderosis: detection and clinical significance in cerebral amyloid angiopathy and related conditions. *Brain*. 2015;138:2126–2139.

Supplemental Tables

Supplemental Table I. Comparison between included and excluded patients

	Included cerebellar-ICH N=128	Excluded cerebellar-ICH N=56	p-value
Mean Age±SD	72.8±12.1	72.8±14.1	0.9
Sex (%)	59 (46)	29 (52)	0.4
Hypertension (%)	109 (85)	46 (82)	0.6
Diabetes (%)	28 (22)	7 (12)	0.1
Hypercholesterolemia (%)	59 (46)	23 (41)	0.5
Atrial Fibrillation (%)	33 (26)	14 (25)	0.9
Warfarin (%)	36 (30)	21 (37)	0.2
Antiplatelets (%)	56 (44)	21 (37)	0.5
Statins (%)	45 (35)	19 (34)	0.8
Previous ischemic stroke (%)	29 (23)	8 (14)	0.2
Previous ICH (%)	7 (5)	3 (5)	1.0
Hematoma evacuation (%)	30 (23)	21 (37)	0.05
ICH volume median (IQR)	6 (2-16)	32 (18-53)	<0.001
30-day mortality	21 (16)	38 (68)	<0.001

SD: standard deviation, ICH: intracerebral hemorrhage; IQR: interquartile range

Supplemental Table II. Definition of cerebellar-ICH according to the location of the primary hematoma

| Cerebellar-ICH pattern	Definition
Deep cerebellar-ICH	The main bulk of the hemorrhage is centered in the deep cerebellum, involving both cerebellar grey nuclei and white matter. The epicenter usually extends in the 2/3 median portion of the cerebellar hemisphere and the hematoma spares or only marginally involves the vermis and cerebellar cortex. A small deep hematoma may also be centered laterally to the upper part of the fourth ventricle within the cerebellar peduncles.
Superficial cerebellar-ICH	The main bulk of the hemorrhage is centered in the superficial cerebellar cortex or at the junction of the cortex and cerebellar white matter. The bulk of the hematoma is generally located in the lateral portion of cerebellar hemisphere lobules and may be responsible for mass effect on cerebellar white matter. In some cases, they can extend medially to the vermis or be confined mostly to the vermis.
Large hematoma with uncertain location	Large hematoma that extends and involved both cerebellar cortex, deep grey nuclei and cerebellar white matter.

Supplemental Table III. Comparison between cerebellar-ICH patients with and without MRI

	Patients with MRI N=80	Patients without MRI N=48	p-value
Mean Age±SD	73.5±10.9	71.5±13.9	0.4
Sex (%)	38 (47)	21 (43)	0.6
Hypertension (%)	66 (82)	43 (89)	0.2
Diabetes (%)	60 (75)	40 (83)	0.3
Hypercholesterolemia (%)	37 (46)	22 (46)	0.9
Atrial Fibrillation (%)	20 (25)	13 (27)	0.8
Warfarin (%)	19 (24)	17 (35)	0.2
Antiplatelets (%)	37 (46)	19 (40)	0.4
Statins (%)	25 (31)	20 (42)	0.2
Previous ischemic stroke (%)	19 (24)	10 (21)	0.7
Previous ICH (%)	6 (7)	1 (2)	0.2
Hematoma evacuation (%)	14 (17)	16 (33)	0.04
ICH volume median (IQR)	4 (2-13)	10 (5-23)	<0.001
30-day mortality (%)	9 (11)	12 (25)	<0.001

SD: standard deviation; ICH: intracerebral hemorrhage; IQR: interquartile range; MRI: magnetic

resonance imaging

Supplemental Figure

Supplemental Figure I. Schematic representation of different cerebellar-ICH locations
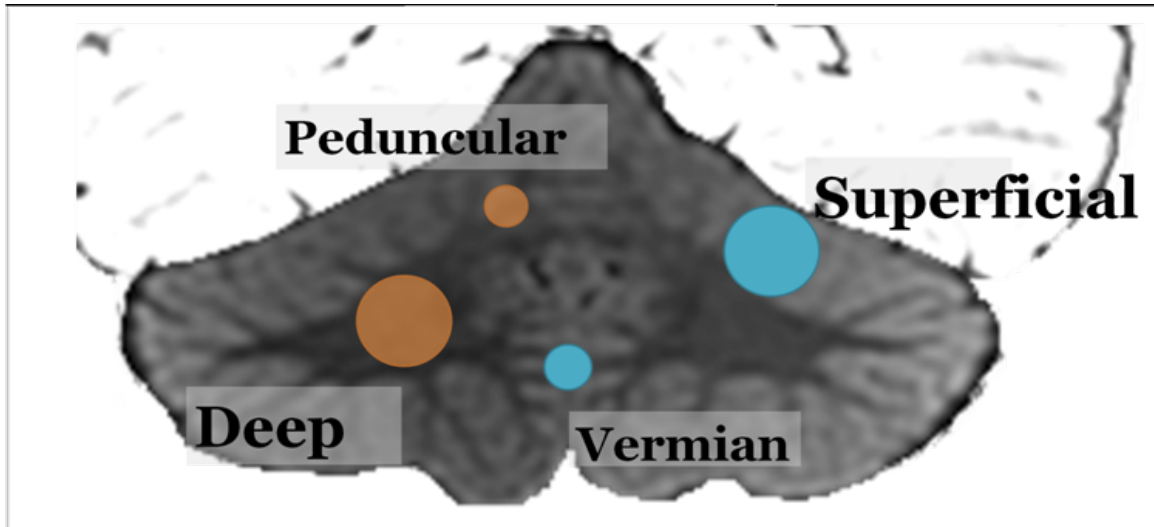
The figure (axial view) schematically represents the location a) deep cerebellar-ICH (with and without peduncular involvement; orange circles); b) superficial cerebellar-ICH (with and without vermian involvement; blue circles).