

Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Characteristics of the current cohort (n = 65)

Variables	
Age, mean ± SD (range)	50.1 ± 8.9 (26-67)
Male, n (%)	7 (10.8)
Hypertension, n (%)	7 (10.8)
Migraine^a, n (%)	16 (24.6)
Menopause^b, n (%)	29 (50.0)
Blood pressure surge, n (%)	28 (43.1)
Possible secondary causes or associated conditions	6 (9.2)
PRES, n (%)	3 (4.6)
ICH, n (%)	1 (1.5)
Ischemic stroke, n (%)	1 (1.5)
Cortical SAH, n (%)	1 (1.5)
Number of total TCH,	5.8 ± 7.6
Headache duration	10.2 ± 7.2
Headache Triggers, n (%)	
Bathing	16 (24.6)
Exertion	10 (15.3)
Cough	4 (6.2)
Defecation	19 (29.2)
Rage	11 (16.9)
Sexual activity	9 (13.8)
Accompanying symptoms, n (%)	
Nausea	33 (50.8)
Vomiting	23 (35.4)
Photophobia	10 (15.4)
Phonophobia	14 (21.5)
Number of magnetic resonance images, mean ± SD (range)	2.5 ± 0.5 (2-3)

^aall were migraine without aura; ^bonly in female.

ICH: intracerebral hemorrhage; PRES: posterior reversible encephalopathy syndrome; TCH: thunderclap headache;

WMH: white matter hyperintensity

eTable 2. Spatial and temporal distribution of white matter hyperintensity lesions during the disease course

WMH volume, cm ³ ; Mean ± SD (range)							
Duration from headache onset, days (Patient No.)		1-7d (18)	8-14d (28)	15-21d (21)	22-28d (23)	29-60d (35)	61-90d (36)
Whole brain		1.65±2.53 (0.00-9.95)	1.27±1.31 (0.13-5.20)	3.05± 4.35 ^a (0.13-16.33)	1.07±0.78 ^b (0.11-2.30)	1.49±1.44 (0.31-5.65)	1.00±0.63 (0.05-2.32)
Periventricular white matter		1.12±1.47 (0.00-5.85)	1.02±1.02 (0.13-4.73)	2.25±3.15 ^a (0.11-11.39)	0.83±0.64 ^b (0.10-1.94)	1.03±1.22 (0.19-5.14)	0.77±0.50 (0.05-1.70)
Deep white matter		0.53±1.08 (0.00-4.10)	0.24±0.40 (0.00-2.02)	0.80±1.31 (0.01-4.94)	0.23±0.27 (0.01-0.86)	0.46±0.70 (0.03-2.36)	0.22±0.18 (0.00-0.69)
Brainstem and cerebellum		0.00±0.01 (0.00-0.04)	0.01±0.03 (0.00-0.17)	0.00±0.01 (0.00-0.03)	0.01±0.02 (0.00-0.06)	0.00±0.01 (0.00-0.02)	0.01±0.02 (0.00-0.08)
Specific anatomical locations							
Frontal	<i>Total</i>	0.86±1.65 (0.00-6.08)	0.57±0.69 (0.07-3.43)	1.39± 2.30 ^a (0.00-8.50)	0.43±0.36 ^b (0.02-1.14)	0.72±0.97 (0.03-3.82)	0.47±0.37 (0.00-1.21)
	<i>Periventricular</i>	0.53±0.71 (0.00-2.70)	0.52±0.61 (0.07-3.05)	1.16±1.81 ^a (0.00-6.56)	0.39±0.33 ^b (0.02-1.05)	0.53±0.80 (0.02-3.38)	0.43±0.36 (0.00-1.13)
	<i>Deep</i>	0.33±0.95 (0.00-3.38)	0.05±0.10 (0.00-0.38)	0.22±0.52 (0.00-1.94)	0.05± 0.07 (0.00-0.20)	0.19±0.48 (0.00-1.92)	0.04± 0.06 (0.00-0.23)
Parietal	<i>Total</i>	0.12±0.34 (0.00-1.11)	0.03±0.07 (0.00-0.29)	0.36±0.90 ^a (0.00-3.32)	0.02±0.04 ^b (0.00-0.13)	0.10± 0.33 (0.00-1.30)	0.03± 0.04 (0.00-0.17)
	<i>Periventricular</i>	0.09± 0.27 (0.00-0.90)	0.02±0.06 ^b (0.00-0.22)	0.10± 0.30 (0.00-1.10)	0.01±0.01 (0.00-0.04)	0.02± 0.06 (0.00-0.24)	0.02±0.04 (0.00-0.14)
	<i>Deep</i>	0.03±0.07 (0.00-0.25)	0.01± 0.02 (0.00-0.07)	0.26±0.61 ^a (0.00-2.22)	0.01±0.04 ^b (0.00-0.12)	0.08±0.32 (0.00-1.30)	0.01± 0.02 (0.00-0.07)
Temporal	<i>Total</i>	0.14±0.33 (0.00-1.29)	0.09±0.15 (0.00-0.62)	0.23±0.43 (0.00-1.57)	0.05±0.05 (0.00-0.17)	0.08±0.13 (0.00-0.55)	0.05±0.05 (0.00-0.19)
	<i>Periventricular</i>	0.14± 0.32 (0.00-1.27)	0.08±0.13 (0.00-0.51)	0.18±0.35 (0.00-1.26)	0.04±0.05 ^b (0.00-0.16)	0.08± 0.13 (0.00-0.55)	0.04±0.04 (0.00-0.14)
	<i>Deep</i>	0.00±0.01 (0.00-0.02)	0.01± 0.03 (0.00-0.15)	0.04±0.09 (0.00-0.31)	0.01±0.01 (0.00-0.04)	0.00±0.01 (0.00-0.03)	0.01±0.01 (0.00-0.05)
Occipital	<i>Total</i>	0.13±0.09 (0.00-0.29)	0.14±0.31 (0.00-1.61)	0.22±0.27 (0.00-0.88)	0.11± 0.10 (0.00-0.26)	0.12±0.11 (0.00-0.43)	0.13±0.13 (0.00-0.49)
	<i>Periventricular</i>	0.00± 0.01 (0.00-0.03)	0.00±0.00 (0.00-0.02)	0.02± 0.16 ^a (0.00-0.20)	0.00±0.01 ^b (0.00-0.02)	0.00± 0.00 (0.00-0.01)	0.00± 0.00 (0.00-0.01)
	<i>Deep</i>	0.13±0.09	0.14±0.31	0.20±0.27	0.11± 0.10	0.12±0.11	0.13±0.13

		(0.00-0.29)	(0.00-1.59)	(0.00-0.88)	(0.00-0.25)	(0.00-0.43)	(0.00-0.49)
WMH volume, cm³; Mean ± SD (range)							
Limbic	<i>Total</i>	0.11±0.13 (0.00-0.56)	0.12±0.13 (0.01-0.52)	0.35±0.56 ^a (0.00-2.00)	0.13±0.19 (0.00-0.63)	0.17±0.24 (0.01-0.93)	0.09±0.07 (0.01-0.24)
	<i>Periventricular</i>	0.09±0.11 (0.00-0.39)	0.10±0.10 (0.01-0.39)	0.29±0.48 ^a (0.00-1.68)	0.08±0.08 ^b (0.00-0.26)	0.12± 0.14 (0.00-0.48)	0.06± 0.05 (0.01-0.18)
	<i>Deep</i>	0.02± 0.04 (0.00-0.17)	0.02± 0.04 (0.00-0.13)	0.06±0.09 (0.00-0.32)	0.05±0.12 (0.00-0.37)	0.05±0.15 (0.00-0.60)	0.02±0.03 (0.00-0.13)
Subcortical	<i>Total</i>	0.28±0.21 (0.00-0.77)	0.31±0.28 (0.04-1.08)	0.50±0.49 (0.00-1.22)	0.33±0.26 (0.04-0.85)	0.30±0.24 (0.05-0.98)	0.23±0.16 (0.01-0.54)
	<i>Periventricular</i>	0.27± 0.20 (0.00-0.77)	0.30±0.27 (0.04-1.01)	0.49± 0.48 (0.00-1.22)	0.32± 0.26 (0.04-0.83)	0.29± 0.24 (0.04-0.95)	0.21±0.14 (0.01-0.45)
	<i>Deep</i>	0.01±0.01 (0.00-0.05)	0.01±0.02 (0.00-0.07)	0.01±0.03 (0.00-0.10)	0.01± 0.01 (0.00-0.03)	0.01±0.01 (0.00-0.04)	0.01±0.03 (0.00-0.09)

^aSignificant increase (p<0.05) compared with the value from the previous time period.

^bSignificant decrease (p<0.05) compared with the value from the previous time period.

eTable 3. Exploratory analyses for the correlation between volume of white matter hyperintensity lesions and vascular parameters throughout the disease course

WMH	LI		PI _{ICA}		RI _{ICA}		MMPI		MMRI		MRIR	
	r	p	r	p	r	p	r	p	r	p	r	p
Whole brain	0.154	0.024	0.256	<0.001	0.258	<0.001	0.264	0.003	0.179	0.045	0.010	0.914
Periventricular	0.236	<0.001	0.279	<0.001	0.273	<0.001	0.325	<0.001	0.236	0.007	-0.027	0.760
<i>Frontal</i>	0.249	<0.001	0.254	0.001	0.248	0.001	0.262	0.004	0.193	0.030	-0.048	0.539
<i>Parietal</i>	0.148	0.029	0.155	0.045	0.154	0.046	0.080	0.381	-0.018	0.841	-0.088	0.321
<i>Temporal</i>	0.270	<0.001	0.221	0.004	0.216	0.005	0.032	0.010	0.176	0.048	-0.018	0.857
<i>Occipital</i>	0.190	0.005	0.175	0.023	0.170	0.028	0.257	0.004	0.227	0.010	0.132	0.139
<i>Limbic</i>	0.049	0.473	0.247	0.001	0.243	0.002	0.294	0.001	0.182	0.041	0.044	0.625
<i>Subcortical</i>	0.177	0.009	0.253	0.001	0.247	0.001	0.344	<0.001	0.236	0.007	-0.028	0.757
Deep	0.059	0.385	0.229	<0.001	0.225	<0.001	0.161	0.076	0.086	0.336	0.082	0.357
<i>Frontal</i>	-0.023	0.741	0.202	0.009	0.200	0.010	0.229	0.011	0.163	0.067	0.011	0.901
<i>Parietal</i>	0.020	0.070	0.042	0.590	0.024	0.755	0.096	0.295	0.034	0.708	-0.094	0.289
<i>Temporal</i>	0.000	0.998	0.160	0.039	0.153	0.048	0.361	<0.001	0.338	<0.001	0.040	0.653
<i>Occipital</i>	0.347	<0.001	0.011	0.892	0.024	0.760	0.104	0.256	0.027	0.763	0.075	0.399
<i>Limbic</i>	-0.018	0.790	0.085	0.275	0.070	0.367	0.177	0.050	0.120	0.179	0.145	0.103
<i>Subcortical</i>	-0.038	0.566	0.222	0.004	0.212	0.006	0.275	0.002	0.208	0.019	0.017	0.848
Brainstem and cerebellum	-0.033	0.742	0.178	0.021	0.171	0.027	0.187	0.039	0.153	0.087	0.049	0.580

MMPI: The mean of pulsatility index in the distal and proximal M1 segment of both middle cerebral arteries; MMRI: The mean of resistance index in the distal and proximal M1 segment of both middle cerebral arteries; MRIR: the mean ratio of resistance index along M1 (distal RI to proximal RI); PI_{ICA}: pulsatility index of internal carotid artery; RI_{ICA}: resistance index of internal carotid artery; r: correlation coefficient.

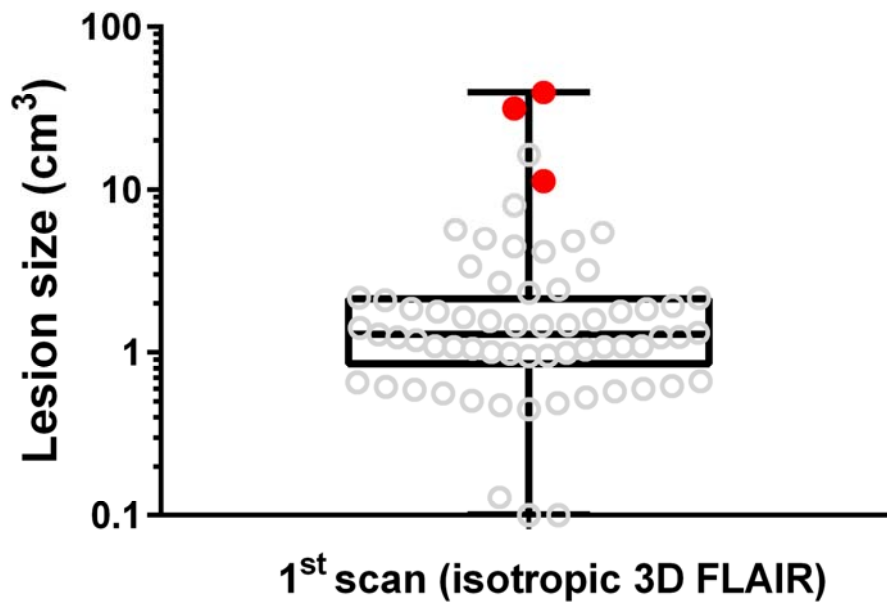
eTable 4. Correlation between clinical variables and the volume of white matter hyperintense lesions (in the initial MRI)

Variables	Total volume of WMH		P value
	+ variable	-variable	
Male	0.57 ± 0.57	1.82 ± 2.47	0.114
Hypertension	1.45 ± 2.53	1.70 ± 2.33	0.771
Migraine^a	2.17 ± 2.07	1.48 ± 2.42	0.231
Menopause^b	2.14 ± 3.17	1.48 ± 1.28	0.263
Blood pressure surge	1.65 ± 3.06	1.70 ± 1.92	0.938
Headache Triggers			
Bathing	1.55 ± 1.79	1.73 ± 2.64	0.802
Exertion	1.21 ± 1.71	1.76 ± 2.55	0.541
Cough	1.81 ± 2.62	1.67 ± 2.46	0.914
Defecation	1.34 ± 1.55	1.81 ± 2.72	0.497
Rage	2.62 ± 4.68	1.49 ± 1.72	0.447
Sexual activity	1.02 ± 1.10	1.83 ± 2.64	0.303
Accompanying symptoms			
Nausea	1.54 ± 1.60	2.32 ± 3.49	0.295
Vomiting	1.20 ± 1.18	2.29 ± 3.16	0.079
Photophobia	1.38 ± 1.67	2.04 ± 2.88	0.492
Phonophobia	1.31 ± 1.47	2.11 ± 2.97	0.357
Clinical parameters			
	Correlation coefficient (r)		P value
Age	0.153		0.183
Number of total TCH	-0.096		0.531
Headache duration	-0.148		0.332
Number of headache triggers	0.011		0.933

^aall were migraine without aura; ^bonly in female.

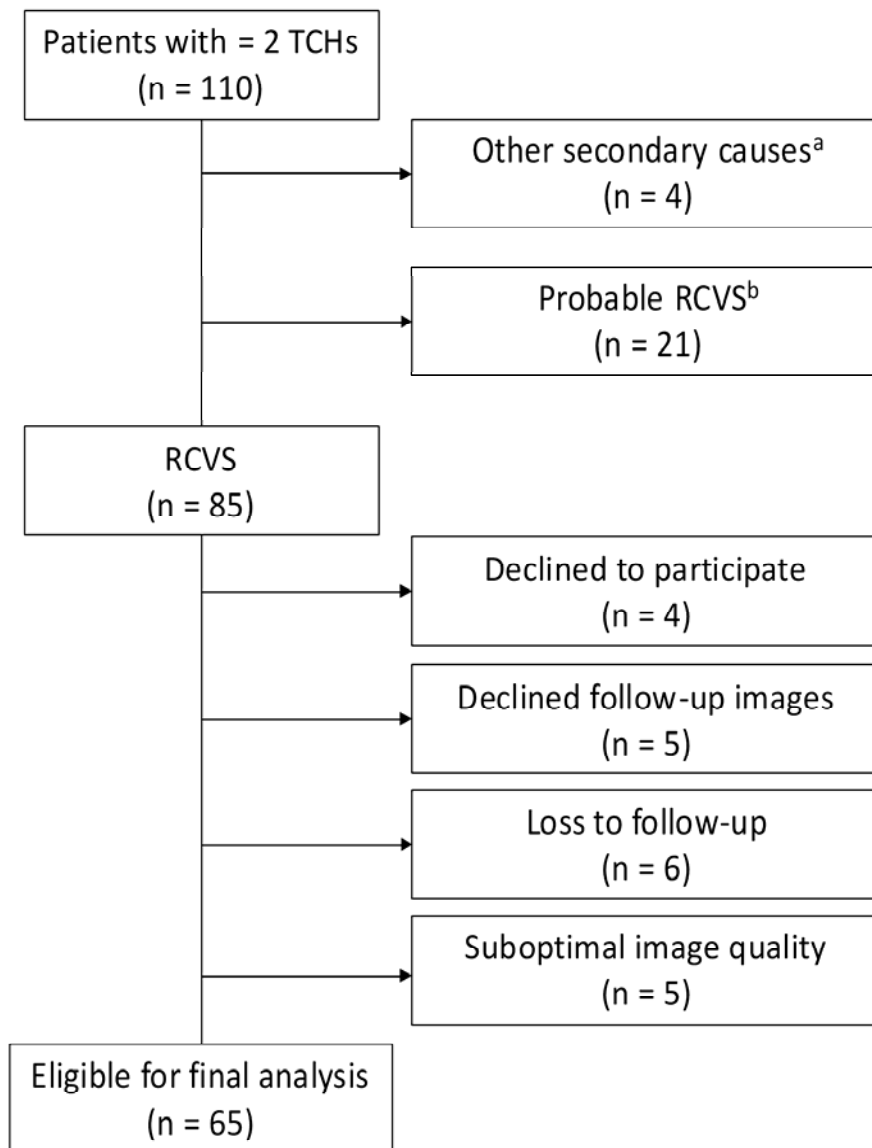
TCH: thunderclap headache; WMH: white matter hyperintensity

eFigure 1. Box plot showing the distribution of the sizes of lesions identified on the first isotropic 3-dimension fluid-attenuated inversion recovery images



Each circle indicates the total lesion volume of each patient. Horizontal lines indicate mean and SDs. The red circles represent the total volumes of those with the PRES lesions that had significant signal changes on apparent diffusion coefficient mapping and diffusion weighted image. The upper and lower ends of the whiskers indicate the maximal and minimal values. Note that the scale of the Y axis is logarithmic.

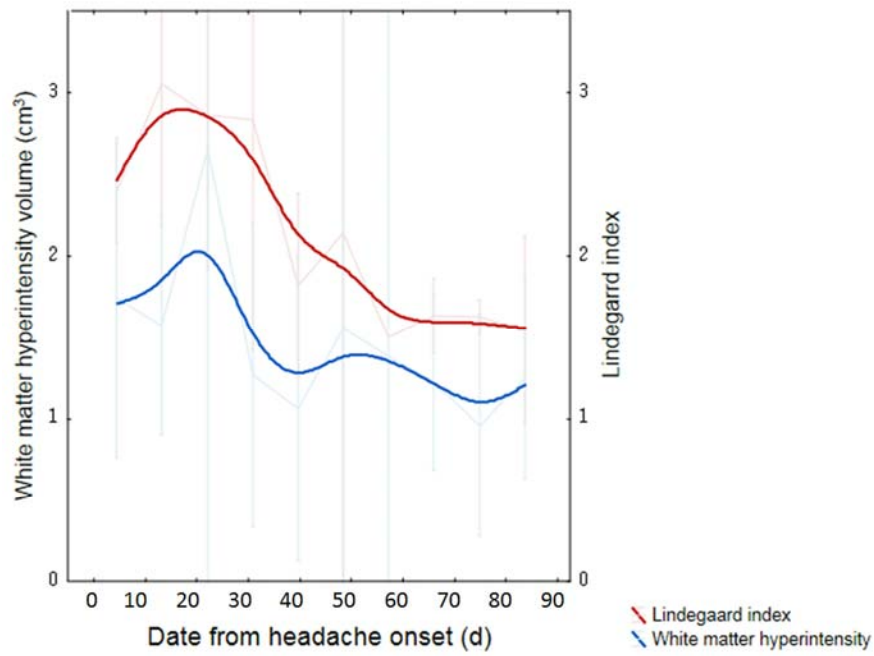
eFigure 2. Diagram of patient screening and enrollment



^aMetastatic brain tumor (n = 2), sphenoid sinusitis (n = 1), aneurysmal subarachnoid hemorrhage (n = 1).

^bTypical thunderclap headaches without significant vasoconstrictions on magnetic resonance angiography.

eFigure 3. Relationship between the white matter hyperintensity lesion load and the severity of vasoconstriction indicated by the Lindegaard index along the disease course



Vertical lines in the background indicates mean \pm standard deviation of white matter hyperintensity loads (blue) and the Lindegaard index (red).