

Supplementary Information

**Cerebral Small Vessel Disease as Imaging Biomarker Predicting
Ocular Cranial Nerve Palsy of Presumed Ischemic Origin at
Admission**

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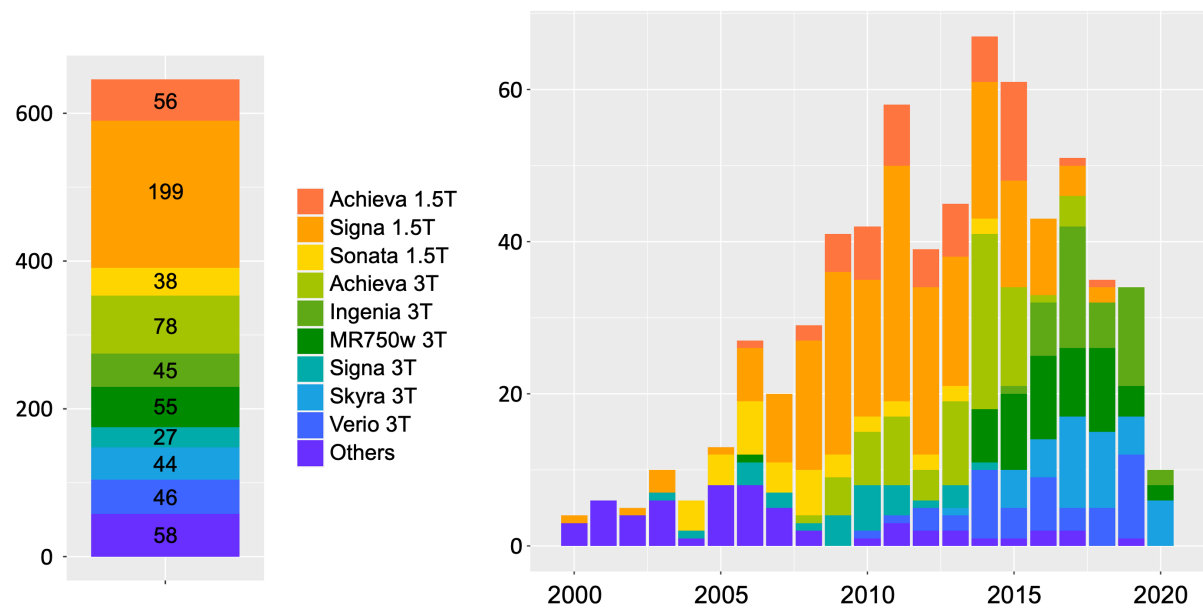
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MRI scanner (n)	Str (T)	Seq	FOV (mm)	TR (ms)	TE (ms)	Thk (mm)	FA (°)	Gap (mm)	IPR (mm)
Philips Achieva (n = 56)	1.5	FLAIR	240×240	11000	120	5	90	1.5	0.5×0.5
		GRE	240×240	810.1	25	5	25	2	0.5×0.5
GE Healthcare SIGNA (n = 199)	1.5	FLAIR	220×220	8802	124.2	5	90	1	0.5×0.5
		GRE	220×220	800	25	5	20	1	0.5×0.5
		SWI	240×240	59	5.9	3	20	0	0.5×0.5
Siemens Sonata (n = 38)	1.5	FLAIR	220×220	9310	130	5	150	1	0.7×0.7
		GRE	220×220	790	25	5	20	1	0.7×0.7
Philips Achieva (n = 78)	3	FLAIR	240×240	11000	120	5	90	1.5	0.5×0.5
		GRE	240×240	717.6	16.1	5	18	2	0.5×0.5
Philips MRI Ingenia Elition (n = 45)	3	FLAIR	220×220	9000	110	5	90	1	0.4×0.4
		SWI	220×220	30	0	2	17	0	0.4×0.4
GE Healthcare Discovery MR750w (n = 55)	3	FLAIR	220×220	9200	126.4	5	160	1	0.4×0.4
		SWI	229×229	37.1	23.2	4	25	-2	0.4×0.4
GE Healthcare SIGNA (n = 27)	3	FLAIR	220×220	9902	163.2	5	90	1	0.4×0.4
		GRE	220×220	467	25	5	20	1	0.4×0.4
Siemens MAGNETOM Skyra (n = 44)	3	FLAIR	220×220	8000	90	5	150	1	0.6×0.6
		SWI	199×219	29	20	2.5	17	0	0.5×0.5
Siemens MAGNETOM Verio (n = 46)	3	FLAIR	187×240	9000	97	5	140	1	0.6×0.6
		SWI	179×239	28	20	3	15	0	0.5×0.5
Siemens MAGNETOM Vision Plus (n = 25)	1.5	FLAIR	240×240	9000	119	5	180	2	0.9×0.9
		GRE	240×240	680	26	5	30	2	0.9×0.9
Siemens MAGNETOM Impact Expert (n = 16)	1.5	FLAIR	220×220	9000	119	6	180	1.2	0.9×0.9
		GRE	220×220	640	26	6	20	2	0.9×0.9
Siemens MAGNETOM Avanto (n = 7)	1.5	FLAIR	199×220	9000	98	5	150	1	0.4×0.4
		GRE	217×240	430	26	5	20	2	0.5×0.5
		SWI	199×220	52	40	2.5	15	0	0.6×0.6
Siemens MAGNETOM Espree (n = 3)	1.5	FLAIR	176×220	7530	125	5	150	1	0.7×0.7
		GRE	178×220	939	26	5	20	1	0.4×0.4
Philips MRI Ingenia (n = 2)	1.5	FLAIR	220×220	9000	110	5	90	1	0.4×0.4
		SWI	220×220	52	0	2	20	0	0.4×0.4
Siemens MAGNETOM Symphony (n = 2)	1.5	FLAIR	178×220	9000	115	5	150	2	0.4×0.4
		GRE	178×220	800	26	5	20	2	0.4×0.4

Siemens MAGNETOM trio A Tim System (n = 3)	FLAIR	199×220	9000	97	5	140	1	0.6×0.6
	SWI	178×220	28	20	2.5	15	0	0.5×0.5

Supplementary Table S1. MRI scanners and imaging acquisition parameters of fluid attenuated inversion recovery (FLAIR), T2*-weighted gradient echo (GRE), and susceptibility weighted images (SWI) were used in this study. Str, field strength; Seq, imaging sequence; FOV, field-of-view; TR, repetition time; TE, echo time; Thk, slice thickness; FA, flip angle; Gap, intersection gap.



Supplementary Figure S1. Distribution of MRI scanners used by year.

	Total (N=646)
WMH	512 (79.3%)
0	134 (20.7%)
1	162 (25.1%)
2	199 (30.8%)
3	48 (7.4%)
4	65 (10.1%)
5	21 (3.3%)
6	17 (2.6%)
PVWMH	374 (57.9%)
0	272 (42.1%)
1	219 (33.9%)
2	98 (15.2%)
3	57 (8.8%)
DWMH	477 (73.8%)
0	169 (26.2%)
1	387 (59.9%)
2	72 (11.1%)
3	18 (2.8%)

Supplementary Table S2. Detailed description of baseline white matter hyperintensities (WMH), periventricular white matter hyperintensities (PVWMH), and deep white matter hyperintensities (DWMH).

Etiology	CN III (n, %)	CN IV (n, %)	CN VI (n, %)	Total (n, %)
Presumed ischemic origin	159 (62.4)	123 (88.5)	191 (75.8)	473 (73.2)
Aneurysm	25 (9.8)	0 (0)	6 (2.4)	31 (4.8)
Cavernous sinus vascular lesions	12 (4.7)	0 (0)	9 (3.6)	21 (3.3)
Infection	3 (1.2)	0 (0)	2 (0.8)	5 (0.8)
Metabolic disorders	0 (0)	0 (0)	1 (0.4)	1 (0.2)
Inflammation	20 (7.8)	2 (1.4)	13 (5.2)	35 (5.4)
Autoimmune	16 (6.3)	6 (4.3)	13 (5.2)	35 (5.4)
Neoplasm	17 (6.7)	7 (5.0)	15 (6.0)	39 (6.0)
Others	3 (1.2)	1 (0.7)	2 (0.8)	6 (0.9)

Supplementary Table S3. Etiologies of the patients with oculomotor (CN III), trochlear (CN IV), and abducens (CN VI) nerves.

	1.5T (N=348)	3T (N=298)	P-value*
Male sex	211 (60.6%)	187 (62.8%)	0.638
Age	66.2 ± 8.8	67.3 ± 8.6	0.126
BMI (kg/m²)	24.4 ± 3.4	24.4 ± 3.7	0.844
Diagnosis			0.43
CN III	144 (41.4%)	111 (37.2%)	
CN IV	76 (21.8%)	63 (21.1%)	
CN VI	128 (36.8%)	124 (41.6%)	
OCNPi	260 (74.7%)	213 (71.5%)	0.403
Periorbital pain or headache	163 (46.8%)	121 (40.6%)	0.131
WMH			0.394
No (0)	77 (22.1%)	57 (19.1%)	
Mild (1–3)	212 (60.9%)	197 (66.1%)	
Moderate to Severe (4–6)	59 (17.0%)	44 (14.8%)	
PVWMH			0.044
0	157 (45.1%)	115 (38.6%)	
Mild (1)	103 (29.6%)	116 (38.9%)	
Moderate to severe (2–3)	88 (25.3%)	67 (22.5%)	
DWMH			0.852
0	93 (26.7%)	76 (25.5%)	
Mild (1)	205 (58.9%)	182 (61.1%)	
Moderate to severe (2–3)	50 (14.4%)	40 (13.4%)	
Silent infarction	83 (23.9%)	69 (23.2%)	0.927
CMBs	39 (12.4%)	47 (18.4%)	0.061
Vascular risk factors	265 (76.1%)	237 (79.5%)	0.35
Hypertension	178 (51.1%)	163 (54.7%)	0.411
Diabetes	148 (42.5%)	128 (43.0%)	0.977
Dyslipidemia	83 (23.9%)	91 (30.5%)	0.069
Smoking	59 (17.0%)	39 (13.1%)	0.209
Ischemic heart disease	38 (10.9%)	24 (8.1%)	0.272
History of stroke	21 (6.0%)	12 (4.0%)	0.329
HbA1c (%)	6.7 ± 1.5	6.7 ± 1.6	0.741
Chronic kidney disease	46 (13.3%)	34 (11.4%)	0.555
eGFR (mL/min/1.73m²)	80.4 ± 24.5	83.8 ± 25.1	0.084
Prior use of antithrombotics	69 (19.9%)	57 (19.2%)	0.903
Follow up duration after OCNP (yr)	5.8 ± 4.3	3.5 ± 3.1	<0.001

Supplementary Table S4. Comparison of clinical and imaging parameters according to the MRI field strength.

BMI, body mass index; CN, cranial nerve; OCNPi, ocular cranial nerve palsy of presumed ischemic origin; WMH, white matter hyperintensities; PVWMH, periventricular white matter hyperintensities; DWMH, deep white matter hyperintensities; CMBs, cerebral microbleeds; eGFR, estimated glomerular filtration rate; OCNP, ocular cranial nerve palsy. Vascular risk factors refer to the presence of at least one of the following: hypertension, diabetes,

dyslipidemia, and/or smoking. *Student's t-test for continuous variables and chi-square test for categorical variables.

	GRE (N = 327)	SWI (N = 244)	P-value*
Male sex	188 (57.5%)	157 (64.3%)	0.116
Age	66.5 ± 8.7	67.3 ± 8.6	0.308
BMI (kg/m²)	24.4 ± 3.6	24.3 ± 3.4	0.704
Diagnosis			0.94
CN III	128 (39.1%)	92 (37.7%)	
CN IV	69 (21.1%)	53 (21.7%)	
CN VI	130 (39.8%)	99 (40.6%)	
OCNPi	237 (72.5%)	181 (74.2%)	0.72
Periorbital pain or headache	157 (48.0%)	121 (49.6%)	0.773
MRI field strength (T)			<0.001
1.5T	236 (72.2%)	80 (32.8%)	
3T	91 (27.8%)	164 (67.2%)	
WMH			0.462
No (0)	69 (21.1%)	52 (21.3%)	
Mild (1–3)	200 (61.2%)	158 (64.8%)	
Moderate to Severe (4–6)	58 (17.7%)	34 (13.9%)	
PVWMH			0.101
0	147 (45.0%)	96 (39.3%)	
Mild (1)	98 (30.0%)	94 (38.5%)	
Moderate to severe (2–3)	82 (25.1%)	54 (22.1%)	
DWMH			0.473
0	81 (24.8%)	68 (27.9%)	
Mild (1)	194 (59.3%)	145 (59.4%)	
Moderate to severe (2–3)	52 (15.9%)	31 (12.7%)	
Silent infarction	75 (22.9%)	58 (23.8%)	0.894
CMBs	37 (11.3%)	49 (20.2%)	0.005
Vascular risk factors	261 (79.8%)	187 (76.6%)	0.418
Hypertension	183 (56.0%)	122 (50.0%)	0.184
Diabetes	146 (44.6%)	100 (41.0%)	0.43
Dyslipidemia	85 (26.0%)	73 (29.9%)	0.346
Smoking	59 (18.0%)	29 (11.9%)	0.058
Ischemic heart disease	29 (8.9%)	29 (11.9%)	0.298
History of stroke	21 (6.4%)	10 (4.1%)	0.305
HbA1c (%)	6.8 ± 1.5	6.6 ± 1.4	0.203
Chronic kidney disease	47 (14.4%)	23 (9.5%)	0.102
eGFR (mL/min/1.73m²)	79.8 ± 24.5	84.8 ± 25.6	0.019
Prior use of antithrombotics	67 (20.5%)	48 (19.8%)	0.931
Follow up duration after OCNP (yr)	5.7 ± 4.3	2.8 ± 2.4	<0.001

Supplementary Table S5. Comparison of clinical and imaging parameters according to susceptibility sequence type GRE, T2*-weighted gradient echo; SWI, susceptibility weighted image; BMI, body mass index; CN, cranial nerve; OCNPi, ocular cranial nerve palsy of presumed ischemic origin; WMH, white matter hyperintensities;

PVWMH, periventricular white matter hyperintensities; DWMH, deep white matter hyperintensities; CMBs, cerebral microbleeds; eGFR, estimated glomerular filtration rate; OCNP, ocular cranial nerve palsy. Vascular risk factors refer to the presence of at least one of the following: hypertension, diabetes, dyslipidemia, and/or smoking.

*Student's t-test for continuous variables and chi-square test for categorical variables.

	OCNPi	
	Odds ratio (95% C.I.)	<i>P</i> -value
Model 4. PVWMH		
No (0)	Reference	Reference
Mild (1)	1.61 (0.92–2.81)	0.093
Moderate to severe (2–3)	1.48 (0.73–3.01)	0.275
Model 5. DWMH		
No (0)	Reference	Reference
Mild (1)	2.26 (1.31–3.91)	0.004
Moderate to severe (2–3)	1.66 (0.72–3.82)	0.233

Supplementary Table S6. Odds ratios of imaging parameters based on multivariate logistic regression analysis. In each model, the covariates were age, sex, diagnosis, MRI field strength (3T vs. 1.5T), body mass index, hypertension, diabetes, ischemic heart disease, estimated glomerular filtration rate, prior use of antithrombotics, and dyslipidemia. OCNPi, ocular cranial nerve palsy of presumed ischemic origin; PVWMH, periventricular white matter hyperintensities; DWMH, deep white matter hyperintensities.

	Total (N = 144)	OCNPi (N = 76)	OCNPo (N = 68)	P-value*
Male sex	76 (52.8%)	50 (65.8%)	26 (38.2%)	0.002
Age	65.0 ± 9.2	66.1 ± 8.9	63.7 ± 9.4	0.114
BMI (kg/m²)	23.3 ± 3.5	23.6 ± 3.1	23.0 ± 3.7	0.354
Diagnosis				0.001
CN III	56 (38.9%)	21 (27.6%)	35 (51.5%)	
CN IV	35 (24.3%)	27 (35.5%)	8 (11.8%)	
CN VI	53 (36.8%)	28 (36.8%)	25 (36.8%)	
WMH				0.033
No (0)	38 (26.4%)	14 (18.4%)	24 (35.3%)	
Mild (1–3)	91 (63.2%)	51 (67.1%)	40 (58.8%)	
Moderate to Severe (4–6)	15 (10.4%)	11 (14.5%)	4 (5.9%)	
PVWMH				0.136
0	76 (52.8%)	35 (46.1%)	41 (60.3%)	
Mild (1)	48 (33.3%)	27 (35.5%)	21 (30.9%)	
Moderate to severe (2–3)	20 (13.9%)	14 (18.4%)	6 (8.8%)	
DWMH				0.057
0	44 (30.6%)	18 (23.7%)	26 (38.2%)	
Mild (1)	87 (60.4%)	48 (63.2%)	39 (57.4%)	
Moderate to severe (2–3)	13 (9.0%)	10 (13.2%)	3 (4.4%)	
Silent infarction	20 (14.0%)	13 (17.3%)	7 (10.3%)	0.332
CMBs	17 (13.9%)	11 (16.9%)	6 (10.5%)	0.45
MRI field strength				0.436
1.5T	83 (57.6%)	41 (53.9%)	42 (61.8%)	
3T	61 (42.4%)	35 (46.1%)	26 (38.2%)	
Susceptibility sequence				0.618
GRE	66 (53.7%)	33 (50.8%)	33 (56.9%)	
SWI	57 (46.3%)	32 (49.2%)	25 (43.1%)	
Ischemic heart disease	6 (4.2%)	4 (5.3%)	2 (2.9%)	0.781
History of stroke	2 (1.4%)	2 (2.6%)	0 (0.0%)	0.526
HbA1c (%)	5.6 ± 0.4	5.6 ± 0.5	5.6 ± 0.3	0.791
Chronic kidney disease	9 (6.3%)	4 (5.3%)	5 (7.4%)	0.879
eGFR (mL/min/1.73m²)	86.5 ± 26.5	84.8 ± 23.7	88.4 ± 29.4	0.432
Prior use of antithrombotics	6 (4.2%)	4 (5.3%)	2 (3.0%)	0.795
Follow up duration after OCNP (yr)	4.8 ± 4.1	5.8 ± 4.2	4.4 ± 4.1	0.141

Supplementary Table S7. Comparison of ocular cranial nerve palsy of presumed ischemic origin (OCNPi) with ocular cranial nerve palsy of other origin (OCNPo) among patients without vascular risk factors. BMI, body mass index; CN, cranial nerve; OCNP, ocular cranial nerve palsy; WMH, white matter hyperintensities; PVWMH, periventricular white matter hyperintensities; DWMH, deep white matter hyperintensities; CMBs, cerebral microbleeds; GRE, T2*-weighted gradient echo; SWI, susceptibility-weighted image; eGFR, estimated glomerular filtration rate. Vascular risk factors refer to the presence of at least one of the following: hypertension,

diabetes, dyslipidemia, and/or smoking. *Student's t-test for continuous variables and chi-square test for categorical variables.