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Shape and Location of Carotid Atherosclerotic Plaque and Intraplaque Hemorrhage:

A High-resolution Magnetic Resonance Imaging Study

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Aim: The present study aimed to investigate the association between shape and location of atherosclerotic plaques and intraplaque hemorrhage (IPH) in carotid arteries using magnetic resonance (MR) imaging.

Methods: Overall, 114 symptomatic patients (mean age: 64.9 ± 10.9 years; 81 males) who underwent MR imaging and had advanced carotid plaques were included in analysis. IPH presence and carotid plaque shape and location (below and above bifurcation) were evaluated. The plaque shape was defined as follows: type-I: the arc-length of plaque is greater in the upstream; type-II: the arc-length of plaque in downstream and upstream is equal; and type-III: the arc-length of plaque is greater in downstream. The plaque shape and location were compared between plaques with and without IPH and their associations with IPH were determined.

Results: Of 181detectedplaques, 57 (31.5%) had IPH. Compared with plaques without IPH, those with IPH had higher incidence of the plaque shape of type-I (66.7% vs. 32.2%, $P<0.001$), lower incidence of plaque shape of type-III (24.6% vs. 50.0%, $P=0.001$), and were more likely located above carotid bifurcation (71.9% vs. 48.4%, $P=0.003$). The plaque shape of type-I (OR, 4.01; 95%CI, 1.36–11.83; $P=0.012$) and location above bifurcation (OR, 3.21; 95%CI, 1.07–9.61; $P=0.037$) of carotid plaques were significantly associated with IPH after adjusting for confounder factors.

Conclusions: Carotid plaque shape and location are significantly associated with the occurrence of IPH. Our findings could provide new insights for the pathogenesis of IPH and vulnerably plaques.

Key words: Carotid artery, Atherosclerosis, Intraplaque hemorrhage, Risk factor, Magnetic resonance imaging

Abbreviations: IPH: intraplaque hemorrhage, MR: magnetic resonance, OR: odds ratio, CI: confidence interval, CEA: carotid endarterectomy, BMI: body mass index, TOF: time-of-flight, FOV: field of view, LRNC: lipid-rich necrotic core, WT_{max}: maximum wall thickness, CCA: common carotid artery, BIF: bifurcation of carotid artery, ICA: internal carotid artery

Introduction

Vulnerable atherosclerotic plaques in carotid arteries have been demonstrated to have a significant correlation with cerebrovascular ischemic events, such as ischemic stroke and transient ischemic attack[1-3]. Intraplaque hemorrhage (IPH), one of compositional characteristics of vulnerable plaques, plays a critical role in stratifying the risk of future events for patients with carotid atherosclerosis[4-6]. The mechanism of

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IPH in carotid plaques remains unclear. It is important to investigate the risk factors for IPH to stabilize atherosclerotic plaque and thereby prevent future cerebrovascular events.

Previous evidences have shown that local factors of atherosclerotic plaques play an important role in the occurrence of carotid IPH. Investigators have demonstrated that the likelihood of IPH increased with an increase of plaque burden as measured by intima-media thickness or plaque volume[7, 8]. In addition, carotid plaque calcification[9, 10] and ulceration[11] have been found to be associated with the presence of IPH. It has been proved that higher maximum shear stresses that act on plaques were independently correlated with occurrence of IPH[12]. The shear stresses may vary with different carotid plaque shape and location because of the change in hemodynamics caused by the turbulent flow in carotid arteries. However, the relationship between IPH and the carotid plaque shape and location remains unclear.

High-resolution multicontrast magnetic resonance imaging (MRI) has been demonstrated to be capable of evaluating location and morphological features of carotid plaques[13, 14]. Furthermore, MRI exhibits excellent capability in characterizing carotid plaque IPH validated by histology[15, 16].

Aim

The present study aimed to investigate the association between IPH and carotid plaque shape and location of carotid plaques using the multicontrast MR imaging techniques.

Methods

Study Population

The study enrolled patients who suffered from recent cerebrovascular ischemic symptoms (within two weeks), including stroke or transient ischemic attack and had atherosclerotic plaque in at least one carotid artery as determined by ultrasound. All patients underwent MR vessel wall imaging examination for bilateral carotid arteries. The exclusion criteria were as follows: 1) contraindication to MR examination; 2) previous history of carotid endarterectomy (CEA); 3) previous history of radiotherapy at neck; and 4) claustrophobia. Demographic and clinical information including age, sex, body mass index (BMI), hypertension, diabetes, hyperlipidemia, lipid levels, smoking history, coronary heart disease, and statin utilization was collected from clinical record. The study protocol conforms to the ethical guidelines of the Declaration of Helsinki and was approved by the Institution's ethics committee for research on humans. All participants provided written consent forms.

Carotid Artery MR Imaging

Carotid MR imaging was performed on a 3.0T MR scanner (Achieva TX, Philips Healthcare, Best, The Netherlands) using a dedicated 8-channel phase array carotid coil. MR imaging parameters for the three-dimensional time-of-flight (TOF) imaging were as follows: repetition time (TR)/echo time (TE) of 29 ms/4.9 ms, field of view(FOV) of 140 mm × 140 mm, flip angle of 20°, matrix size of 256 × 256, and slice thickness of 2 mm. Parameters for two-dimensional T1-weighted (T1W) quadruple inversion recovery imaging were as follows: TR/TE of 800 ms/10 ms, FOV of 140 mm × 140 mm, flip angle of 90°, matrix size of 256 × 256, and slice thickness of 2 mm and those for axial T2-weighted (T2W) multislice double inversion recovery imaging were as follows: TR/TE of 4800 ms/50 ms, FOV of 140 mm × 140 mm, flip angle of 90°, matrix size of 256 × 256, and slice thickness of 2 mm. The MR scan was centered to the bifurcation of the symptomatic side of carotid artery.

MR Image Analysis

The MR vessel wall images of symptomatic carotid arteries were reviewed by two radiologists with > 2 years' experience in cerebrovascular imaging using custom-designed software CASCADE (Vascular Imaging Lab, University of Washington)[17] with consensus. A 4-point scale (1 = poor, 2 = marginal, 3 = good, and 4 = excellent) was utilized to assess the image quality per slice[18], and images with quality score < 2 were excluded from the study. The lumen and wall boundaries were manually outlined and the lumen area, wall area, and maximum wall thickness (WT_{max}) were measured. The presence or absence of ulceration and plaque compositions, such as lipid-rich necrotic core (LRNC), IPH, and calcification, were determined[16]. Only advanced carotid plaques with compositions, such as LRNC, IPH, calcification, or ulceration, were included for further analysis. Carotid plaques were classified as type-I, type-II, and type-III according to the symmetric features of the plaque shape in the longitudinal direction (**Fig. 1**): instances where in the greater arc-length of carotid plaques was located in the downstream arterial wall above the location of WT_{max} were classified as type-I; instances where in the arc-length of carotid plaques in downstream and upstream arterial wall from the location of WT_{max} was equal were classified as type-II; instances where in the greater arc-length of carotid plaques was located in upstream arterial wall below the location of WT_{max} were classified as type-III. When the surface of carotid

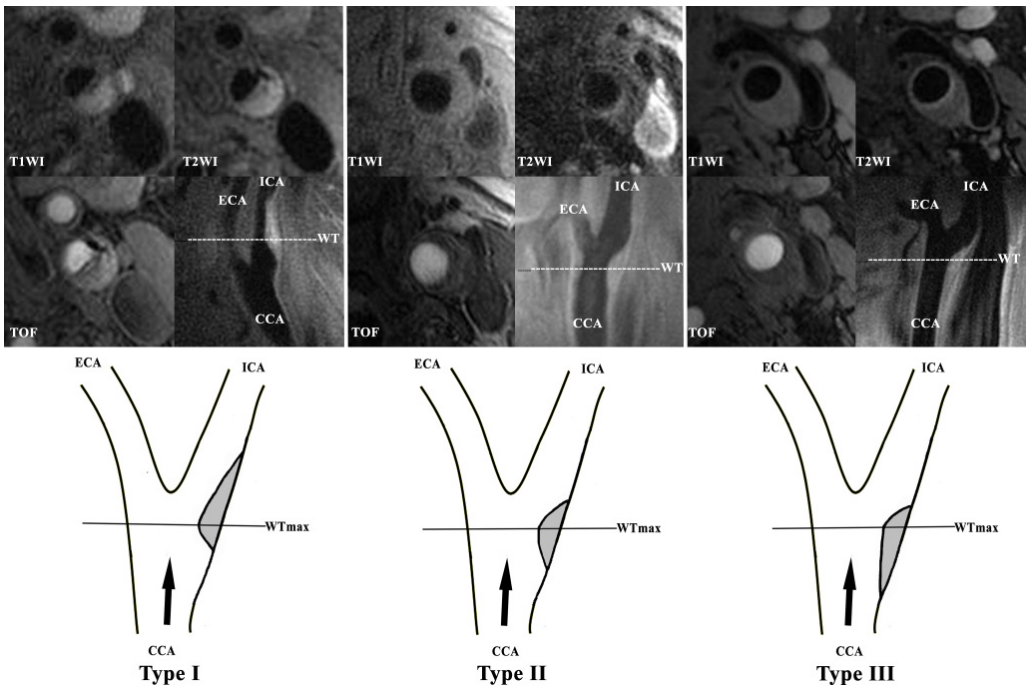

Fig. 1. Examples of different types of plaque shape

T1W images (the top row) and their corresponding diagrams (the bottom row) of the three shape types are shown. Type-I was defined when the greater arc-length of carotid plaques was located in the downstream arterial wall above the location of WT_{max}; MR images show that the carotid plaque has IPH (high-intensity on all the sequences), LRNC (iso-intensity on T1WI and low-intensity on T2WI), and calcification (low-intensity on all the sequences). Type-II was defined if the arc-length of carotid plaques in downstream and upstream arterial wall from the location of WT_{max} was equal;. Furthermore, MR images show that the carotid plaque had LRNC (iso-intenstiy on T1WI and low-intensity on T2WI). Type-III was defined if the greater arc-length of carotid plaques was located in upstream arterial wall below the location of WT_{max}.MR images show that the carotid plaque had LRNC (iso-intenstiy on T1WI and low-intensity on T2WI). (WT_{max}: maximum wall thickness; ICA: internal carotid artery; ECA: external carotid artery; CCA: common carotid artery; BIF: bifurcation of carotid artery; Black arrow: direction of blood flow; IPH: intraplaque hemorrhage; LRNC: lipid-rich necrotic core).

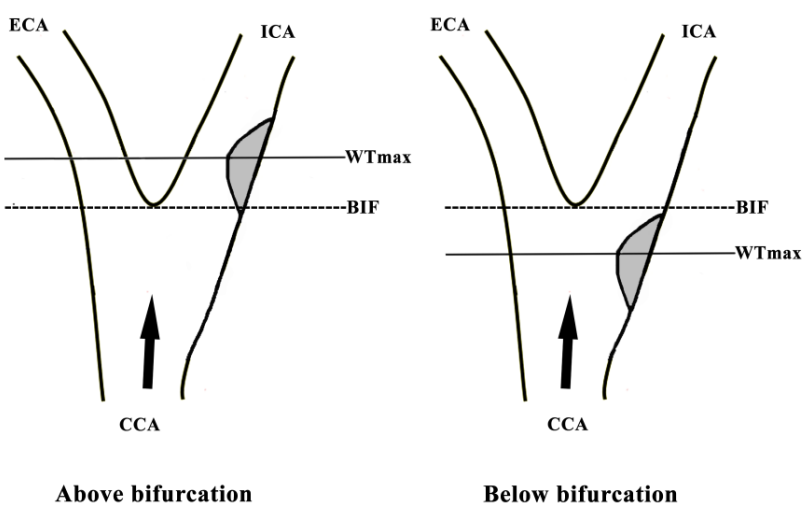

Fig. 2. Diagram of location of carotid plaques

Plaques located above bifurcation and below bifurcation are defined according to the location of the WT_{max} of carotid plaque (WT_{max}: maximum wall thickness; ICA: internal carotid artery; ECA: external carotid artery; CCA: common carotid artery; BIF: bifurcation of carotid artery; Black arrow: direction of blood flow)

Table1. Comparison of patients'clinical characteristics between plaques with and without IPH

	Mean ± SD or *n* (%)		*P*
	With IPH (*n*=57)	Without IPH (*n*=124)	
Gender, male	46 (80.7)	85 (68.5)	0.089
Age, y	68.7 ± 11.1	63.3 ± 10.2	0.298
BMI kg/m^2	24.3 ± 3.3	24.1 ± 3.0	0.461
Hypertension	44 (77.2)	92 (74.2)	0.665
Hyperlipidemia	29 (50.9)	71 (57.3)	0.423
Diabetes	18 (31.6)	50 (40.3)	0.259
CHD	9 (15.9)	28 (22.6)	0.720
Low density protein, mmol/L	2.5 ± 0.89	3.0 ± 1.0	0.720
High density protein, mmol/L	1.0 ± 0.2	1.0 ± 0.3	0.793
Total density protein, mmol/L	4.0 ± 0.9	4.5 ± 1.0	0.977
Triglyceride, mmol/L	1.3 ± 0.4	1.5 ± 0.5	0.360
Statin use	15 (26.3)	60 (48.4)	0.005
History of smoke	39 (68.4)	60 (48.4)	0.012

IPH: intraplaque hemorrhage; SD: standard deviation; BMI: body mass index; CHD: coronary heart disease.

plaques was irregular, the arc-length was estimated using smoothing algorithm. The location of carotid plaques was divided into two categories—above bifurcation and below bifurcation—that were defined according to the location of WT_{max} of carotid plaque (**Fig. 2**).

Statistical Analysis

The continuous variables are presented as mean ± standard deviation (SD) and categorical variables are expressed as percentage. The clinical characteristics and carotid plaque measurements were compared between plaques with and without IPH using independent Student *t*-test or chi-square test. Logistic regression analysis with generalized estimating equation correction was used to calculate the odds ratio (OR) and corresponding 95% confidence interval (CI) of carotid plaque shape and location in discriminating presence of IPH. Two-sided $p<0.05$ was considered significant; statistical analyses were performed using the software of SPSS 22.0 (IBM, Chicago, IL).

Results

Overall, 131 patients with complex carotid plaque compositions were enrolled in the study from May 2010 to August 2015. Of these, 17patients were excluded because of poor image quality ($n=5$) and insufficient longitudinal coverage ($n=12$). Among the remaining114 patients, mean age was 64.9 ± 10.9 years old, 81 (71.1%) were males, 44 (38.6%) had diabetes mellitus, 87 (76.3%) had hypertension, 65 (57.0%) had history of smoking, 64 (56.1%) had hyperlipidemia, and 48 (42.1%) used statins. **Table 1** shows the clinical characteristics of the population.

Imaging Characteristics of Carotid Atherosclerotic Plaque

Of 114 patients, 67 (58.8%) had bilateral carotid plaques and 47 (41.2%) had unilateral carotid plaques. Among all 181detected plaques, 174 (96.1%) had LRNC, 57 (31.5%) had IPH, 121 (66.9%) had calcification, and 16 (8.8%) had ulceration. The maximum wall thickness, stenosis, and mean wall area of carotid arteries were 3.7 ± 1.7 mm, 28.2% ± 35.5%, and 35.9 ± 11.1 mm^2, respectively.

Compared with plaques without IPH, those with IPH had greater maximum wall thickness (5.1 ± 1.9 mm vs. 3.1 ± 1.1 mm, $P<0.001$), mean wall area (44.9 ± 12.5 mm^2 vs. 31.7 ± 7.4 mm^2, $P=0.001$), and stenosis (50.4% ± 39.1% vs.18.0% ± 28.5%, $P<0.001$), had higher incidence of plaque shape of type-I (66.7% vs. 32.2%, $P<0.001$) and lower incidence of plaque shape of type-III (24.6% vs. 50.0%, $P=0.001$),and were more likely to be located above the bifurcation of carotid arteries (71.9% vs. 48.4%, $P=0.003$) (**Table 2**).

Association between Carotid Plaque Shape and Location and IPH

Univariate logistic regression analysis showed that the plaque shape of type-I (OR, 4.11; 95%CI, 1.95–8.63; $P<0.001$) and type-III (OR, 0.33; 95%CI, 0.17–0.65; $P=0.001$) and location above bifurcation (OR, 3.28; 95%CI, 1.40–7.67; $P=0.006$) of carotid plaques were significantly associated with

Table 2. Characteristics of burden, compositions, shape and location of carotid plaques between plaques with IPH and without IPH

	Mean ± SD or n (%)		*P*
	With IPH (*n* = 57)	Without IPH (*n* = 124)	
Plaque burden and compositions			
Mean total vessel area	82.4 ± 16.4	73.0 ± 20.7	0.114
Stenosis	50.4 ± 39.1	18.0 ± 28.5	< 0.001
Mean wall area	44.9 ± 12.5	31.7 ± 7.4	0.001
Maximum wall thickness	5.1 ± 1.9	3.1 ± 1.1	< 0.001
Lipid-rich necrotic core	57 (100.0)	117 (94.3)	0.067
Calcification	44 (77.2)	79 (63.7)	0.071
Ulceration	12 (21.1)	4 (3.2)	< 0.001
Shape of carotid plaque			
Type-I	38 (66.7)	40 (32.2)	< 0.001
Type-II	5 (8.8)	22 (17.7)	0.116
Type-III	14 (24.6)	62 (50.0)	0.001
Location of carotid plaque			
Above bifurcation	41 (71.9)	60 (48.4)	0.003
Below bifurcation	16 (28.1)	64 (51.6)	

IPH: intraplaque hemorrhage; SD: standard deviation

Table 3. Logistic regression hazard models of risk factors for the presence of IPH

	Presence of IPH								
	Univariate regression			Model 1*			Model 2†		
	OR	95%CI	*P*	OR	95%CI	*P*	OR	95%CI	*P*
Shape									
Type-I	4.11	1.95–8.63	< 0.001	4.26	1.41–11.25	< 0.001	4.01	1.36–11.83	0.012
Type-II	0.50	0.21–1.18	0.114	0.45	0.15–1.31	0.141	0.39	0.11–2.34	0.515
Type-III	0.33	0.17–0.65	0.001	0.29	0.13–0.65	0.003	0.46	0.18–1.11	0.119
Location									
Above BIF	3.28	1.40–7.67	0.006	4.02	1.48–10.95	0.006	3.21	1.07–9.61	0.037

IPH: intraplaque hemorrhage; OR: odds ratio; BIF: bifurcation of carotid artery. Model 1 is adjusted for age, sex, smoking history, and statin use; Model 2 is adjusted for age, sex, smoking history, statin use, maximum wall thickness, stenosis, and ulceration.

the presence of IPH. Adjusting for clinical confounding factors, including age, sex, smoking history, and statin utilization, revealed a significant association of plaque shape of type-I (OR, 4.26; 95%CI, 1.41–11.25; $P<0.001$) and type-III (OR, 0.29; 95%CI, 0.13–0.65; $P=0.003$)and location above bifurcation(OR, 4.02; 95%CI, 1.48–10.95; $P=0.006$) with IPH. After further adjustment for maximum wall thickness, stenosis of carotid artery, and ulceration, the association of plaque shape of type-I (OR, 4.01; 95%CI, 1.36–11.83; $P=0.012$) and location above bifurcation (OR, 3.21; 95%CI, 1.07–9.61; $P=0.037$) with IPH remained significant (**Table 3**).

Discussion

The present study investigated the relationship between the shape and location of carotid atherosclerotic plaque and the presence of IPH. We found that compared with plaques without IPH, those with IPH had higher incidence of plaque shape of type-I, lower incidence of shape of type-III and were more likely to be located above the bifurcation of carotid arteries than those without IPH. In addition, we found that the plaque shape of type-I and location above bifurcation of carotid plaque were significantly associated with the presence of IPH after adjusting for con-

founding factors. Our findings indicate that carotid plaque shape and location might be potential indicators for IPH in symptomatic patients.

In the present study, we found that compared with patients without IPH in carotid plaques, those with IPH were significantly less likely to use statins but more likely to smoke. Our findings are consistent with previous studies[19, 20]. Derksen *et al.*[20] have demonstrated that IPH in carotid plaques was less frequently detected in patients who used statins ($P=0.002$) and statins usage was independently associated with carotid IPH (OR, 0.52; CI, 0.32–0.85; $P=0.009$). It is known that statins could inhabit inflammatory status and biological activity related with inflammation in plaques. Furthermore, neovasculature formation within plaques could be reduced by statins usage. The reduction of inflammation and angiogenesis might play a key role in a decrease of IPH in carotid plaques[19, 21]. In the present study, we observed a higher incidence of smoking in patients with carotid IPH, supporting earlier results of a Rotterdam study by Van *et al.*[22]. They found that current smokers were more likely to have IPH in plaques (OR, 1.6; CI, 1.2–2.3), suggesting that smoking might be a dependent indicator of carotid IPH in patients with carotid atherosclerosis. The nicotine in cigarettes could accelerate the heart rate and elevate the blood pressure of patients. A previous study has reported that elevated blood pressure would increase the risk of IPH in carotid arteries (OR, 1.4; CI, 1.1–1.8)[22].

Our data have shown that the carotid plaque shape of type-I was independently associated with the occurrence of IPH. The mechanism of the relationship between the plaque shape and IPH presence remains unclear. However, plaques with different shapes had different flow biomechanical features acting on their surface that could contribute to the different incidence rates of IPH. In a previous study, Tuenter et al have found that higher maximum shear stresses on plaque surface were independently associated with the presence of carotid IPH (OR, 12.14; 95%CI, 3.21–45.94; $P=0.001$)[12]. Moreover, another study by Huang et al has shown that the value of mean plaque wall stress from hemorrhage parts of plaque was higher than that from non-hemorrhage parts (75.6 vs. 68.1 kPa, $P=0.003$)[23]. The possible mechanism could be that higher maximum shear stress accelerates the expression of vascular endothelial growth factor, which will induce angiogenesis, disrupt the vascular barrier function in plaques, and subsequently lead to the occurrence of IPH in plaques[24]. In the present study, compared with plaques with shape of type-II and type-III, those with shape of type-I had the higher slope toward the upstream and might suffer a higher shear stress which would stimulate the occurrence of carotid IPH[25].The mechanism of the relationship between the plaque shape and IPH needs further investigation.

Furthermore, in the present study, we observed that carotid plaques located above the bifurcation of carotid artery were more likely to have IPH. However, the underlying mechanism of the location of plaques affecting the occurrence of IPH remains unclear. It has been demonstrated that individual segments of extracranial carotid artery, including common carotid artery (CCA), BIF, and internal carotid artery (ICA), have unique histological[26] and anatomic features[27] and were differently exposed to turbulent flow[28]. The different types of turbulent flow and hemodynamic characteristics between segments above and below carotid bifurcation might result in the different incidence of carotid IPH. In addition, plaques located at different segments of carotid arteries have been demonstrated to have different progression rate. A previous study by Mackinnon *et al.*[29] has shown that the progression rate of carotid plaques at the ICA was significantly greater compared with the CCA. Previous studies have demonstrated that IPH could accelerate the progression of carotid plaques[30, 31]. This suggests that the higher incidence of IPH above BIF in the present study is a contributor of higher progression rate of carotid plaques located at the ICA.

Several limitations in our study should be noted. First, only qualitative evaluation was performed to characterize the carotid plaque shape because of the limitation of two-dimensional imaging techniques utilized in the present study. In recent years, three-dimensional MR vessel wall imaging techniques have been proposed for characterization of carotid plaques with isotropic high spatial resolution and large longitudinal coverage[32, 33] that allow accurate quantification of plaque morphology. These three-dimensional vessel wall imaging techniques could potentially be used to quantitatively evaluate plaque shape, such as the value of the slope of plaque surface. Second, in the present study, because of limited longitudinal coverage, the location of carotid plaques was classified into only two categories according to their location to carotid bifurcation. Future studies are warranted to investigate the relationship between IPH and carotid plaque located in the more proximal segments of CCA or more distal segments of ICA as long as large coverage imaging data available. Third, the hemodynamic characteristics of carotid arteries may play important role in occurrence of carotid IPH. To determine the hemodynamic features in carotid plaques with different shape and location patterns could be helpful for better understanding their relationship with carotid

IPH.

Conclusion

Carotid plaque shape and location are independently associated with the occurrence of IPH. Our findings may provide new insights for the pathogenesis of IPH and vulnerably plaques.

Acknowledgments

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Conflicts of Interest

None.

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