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허혈성 뇌졸중 환자에서 죽상경화성 혈관 병변 유무와 Apolipoprotein E 유전자 다형성의 관련성

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Apolipoprotein E Polymorphism in Ischemic Stroke Patients with Different Pathogenetic Origins

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Background : The association of apolipoprotein E (apoE) polymorphism with interindividual variability of serum lipid concentrations and the initiation and progression of atherosclerosis is inconclusive. This study was performed to explore the associations of apoE with lipid concentrations and ischemic stroke in patients with large artery atherosclerosis (LAA) subgroup or without atherosclerotic vascular lesions (small artery occlusion, SAO) subgroup through a case-control study among the Korean population.

Methods : The ischemic stroke group (n=194) was subdivided into an LAA subgroup (n=112) and a SAO without atherosclerotic lesion subgroup (n=82). An age-matched healthy control group (n=168) was recruited. Serum lipid concentrations were measured and apoE genotypes were determined by real-time PCR and melting curve analysis with the LightCycler (Roche Diagnostics).

Results : The frequency of the ε4 carriers was significantly higher in the ischemic stroke group (22.7%) than in the control group (11.9%) (P=0.01). However, the frequency of ε4 carriers showed no difference between the LAA and SAO subgroups (22.3% vs 23.2%, P=0.89). The adjusted low density lipoprotein cholesterol (LDLc) concentration was significantly higher in ischemic stroke group than in control group (P=0.04), but showed no significant differences in all lipid concentrations between the LAA and SAO subgroups. LDLc concentrations were lower in ε2 carriers than in ε3 and ε4 alleles, but showed no difference between the ε4 carriers and ε3 allele.

Conclusions : Although there was an association between the ε4 allele and ischemic stroke and between the LDLc concentration and ischemic stroke, there was no significant difference in the lipid concentrations and distribution of apoE genotypes between the LAA and SAO subgroups. Therefore, the ε4 allele may have different effects on the ischemic stroke that are independent of the atherosclerotic mechanism by high LDLc concentration. *(Korean J Lab Med 2006;26:210-6)*

Key Words : *Apolipoprotein E polymorphism, Ischemic stroke, Lipid concentrations*

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INTRODUCTION

Apolipoprotein E (apoE) is a 299 amino acid protein that is encoded by a gene on chromosome 19q13.2 in linkage with genes encoding other apolipoproteins[1]. ApoE is polymorphic, with three common epsilon (ε) alleles: ε2,

ε3, and ε4, resulting in six common genotypes[1, 2]. ApoE ε4 differs from ε3 by a single amino acid substitution at codon 112 (Cys→Arg) and from ε2 by a single amino acid substitution at codon 158 (Arg→Cys)[3]. The apoE ε3/ε3 genotype is predominant and the behavior of this form of apoE is accepted as the reference for all apoE-dependent functions. ApoE is known to play a central role in determining the metabolic fate of plasma lipoproteins and consequently of cholesterol[4-7] and to result in interindividual variability in plasma total cholesterol (TC) and low density lipoprotein cholesterol (LDLc) [6-12]. It has been postulated that certain apoE alleles are risk factors for the initiation and/or development of atherosclerosis[13, 14]. However, there are much controversies in the literature with regard to the association of the apoE polymorphism with TC and LDLc levels and we still do not understand the mechanisms by which specific apoE alleles affect atherosclerosis.

Many investigators have reported an association between the ε4 allele and ischemic stroke as they found a higher frequency of the ε4 allele in patients with ischemic stroke than in healthy controls[3, 15-18]. However, not all studies support this association between the ε4 allele and ischemic stroke and there is still controversy over this point [1, 19-23].

Therefore, the aims of this study were 1) to investigate whether apoE polymorphisms play a role in atherosclerosis by comparing the differences between ischemic stroke subgroups with or without atherosclerotic lesions, 2) to study the relationship of lipid profile with apoE polymorphism as a risk factor for vascular event in ischemic stroke group.

SUBJECTS AND METHODS

1. Ischemic stroke patients and controls

Subjects were recruited from the ischemic stroke patients that were admitted to the Department of Neurology of Kyung Hee University Hospital between January 2002 and April 2003. All patients had been diagnosed with ischemic stroke, clinically by history taking and laboratory examinations for the risk factors of vascular disease, and radiologically by magnetic resonance image and angiography. Patients with evidence of cardioembolism were excluded from this study. Finally, 194 ischemic stroke patients, aged 34 to 86 years, were enrolled in the ischemic stroke group. In order to investigate a potential association between apoE polymorphisms and ischemic stroke with atherosclerotic vascular lesion, the patients were classified into two subgroups. Classification was based on the Trial of Org 10172 in Acute Stroke Treatment criteria[24]: i) the large artery atherosclerosis (LAA) group in which subjects had atherothrombotic infarction with atherosclerotic vascular lesion in multiple or single vessels, ii) the small artery occlusion (SAO) group in which subjects were without atherosclerotic vascular lesions. Risk factors were carefully documented: sex, age, hypertension, diabetes, smoking, ischemic heart disease, and family history or past history of stroke.

The control group consisted of 168 age-matched healthy subjects who had visited the Health Examination Center and Neurology Out-patients Clinic. All selected individuals were free from hypertension, diabetes, atherosclerotic peripheral arterial disease, history of previous stroke and ischemic heart disease, and Alzheimer's disease and other degenerative diseases.

Written informed consent was obtained from all subjects, and the study was approved by the institution's research ethical committee.

2. Measurement of lipids

The lipid profile included the serum level of TC, LDLc, high density lipoprotein cholesterol (HDLc), and triglycerides (TG). Venous blood sampling for lipid profile test was performed in the morning after overnight fasting. Especially in ischemic stroke patients, blood sampling for measurement of lipids was done 3 months after the stroke. The lipid profiles were measured with an automated chemistry analyzer Hitachi 7600 (Hitachi, Tokyo, Japan).

3. ApoE genotyping using real time PCR and melting curve analysis

Genomic DNA was extracted and purified from 100 μL of whole blood from each stroke patient and control subject, using an automated nucleic acid isolation and purification system (Magtration System 6GC; Precision System Science, Chiba, Japan) according to the manufacturer's instructions. ApoE genotyping was performed using a com-

mercially available LightCycler ApoE Mutation Detection kit (Roche Diagnostics, Mannheim, Germany), which uses real time PCR and melting curve analysis with the LightCycler (Roche Diagnostics).

Briefly, after preparation of the reaction mixture according to the manufacturer's instructions, 18 μL of the reaction mixture and 2 μL of the isolated genomic DNA template or the positive or negative control were loaded into precooled LightCycler glass capillaries. Sealed capillaries were centrifuged and then placed in the LightCycler rotor. The cycling program consisted of a 60 sec initial denaturation at 95℃, and 45 cycles of denaturation at 95℃ for 0 sec, annealing at 60℃ for 10 sec, and extension at 72℃ for 10 sec. After amplification was completed, genotypes were determined by a melting curve analysis according to the melting behavior of detection probes covering the polymorphic codons by cooling to 42℃ for 4 minutes and then heating slowly at 0.1℃/sec to 80℃. When a mutation is present, the mismatch between the mutation probe and the target destabilizes the hybrid and consequently results in a lower *T*m.

Table 1. Distribution of apoE genotypes and serum lipid concentrations in the control group and the ischemic stroke group

Characteristics	Control group	Stroke group	*P**
Number	168	194	
Sex (M:F)	94:74	116:78	0.46
Age	62.3 (±6.3)	62.0 (±9.5)	0.66
Genotype†			
ε2/ε2	2 (1.2%)	0 (0.0%)	0.13
ε2/ε3	18 (10.7%)	24 (12.4%)	0.62
ε3/ε3	128 (76.2%)	126 (64.9%)	0.02
ε3/ε4	19 (11.3%)	44 (22.7%)	0.00
ε4/ε4	1 (0.6%)	0 (0.0%)	0.28
Carrier†			
ε2 carrier	20 (11.9%)	24 (12.4%)	0.89
ε3 carrier	128 (76.2%)	126 (64.9%)	0.03
ε4 carrier	20 (11.9%)	44 (22.7%)	0.01
Lipid profile‡			
Cholesterol (mg/dL)	193.5 (187.3-199.7)	199.9 (194.3-205.6)	0.19
Triglyceride (mg/dL)	148.3 (132.7-163.9)	146.0 (131.9-160.2)	0.85
HDLc (mg/dL)	44.5 (42.4-46.7)	42.1 (40.2-44.0)	0.15
LDLc (mg/dL)	119.3 (113.5-125.0)	128.6 (123.4-133.9)	0.04

*Two sample t-test for continuous variables and chi-square test for nominal variables between the control group and the ischemic stroke group; †Significant differences in distribution of apoE genotype and apoE carrier between the control group and the ischemic stroke group (χ^2=12.0, 4 d.f., *P*=0.02 and χ^2=6.7, 2 d.f., *P*=0.04, respectively); ‡Mean lipid values are adjusted for sex, age, diabetes, hypertension and smoking, with 95% confidence interval in parenthesis.
Abbreviations: HDLc, high density lipoprotein cholesterol; LDLc, low density lipoprotein cholesterol.

4. Statistical analysis

The differences between the ischemic stroke group and control group and between the LAA and SAO subgroups were compared by the chi-square test for nominal variables and the Student's *t* test for continuous variables. Analysis of Covariance (ANCOVA) with Bonferroni multiple comparison was performed using a general linear model procedure on serum lipid concentrations. To exclude the confounding effect, serum lipid concentrations were adjusted for potential confounders such as sex, age, hypertension, diabetes mellitus, and smoking. The statistical analyses were performed using SPSS for Windows version 11.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

1. Distribution of apoE genotypes and serum lipid concentrations

There were no significant differences in age and sex between the ischemic stroke and the control groups (Table 1). The frequencies of apoE genotypes (and apoE carriers) in the control and ischemic stroke groups are shown in Table 1. There were significant differences in the distribution of apoE genotype and apoE carriers between the ischemic stroke and control groups (χ^2=12.0, 4 d.f., *P*=0.02 and χ^2=6.7, 2 d.f., *P*=0.04). The frequency of the ε4 carriers was significantly higher in the ischemic stroke group (22.7%) than in the control group (11.9%) (*P*=0.01). However, the frequency of the ε2 carriers showed no significant difference between the ischemic stroke (12.4%) and control groups (11.9%) (*P*=0.89). The adjusted LDLc concentration was significantly higher in the ischemic stroke group than in control group (*P*=0.04). Though statistical significance was not found, the adjusted HDLc was apparently lower in the ischemic stroke group than in the control group.

There were no significant differences in the clinical characteristics such as sex, hypertension, diabetes, and smoking between the LAA and SAO subgroups (Table 2). No significant differences were found in the distribution of apoE genotypes and apoE carriers between the LAA and SAO subgroups (χ^2=13.8, 8 d.f., *P*=0.09 and χ^2=8.4, 4 d.f., *P*=0.08). The frequency of the ε4 carriers showed

Table 2. Distribution of apoE genotypes and serum lipid concentrations in the LAA subgroup and the SAO subgroup

Characteristics	LAA	SAO	P^*
Number	112	82	
Sex (M:F)	67:45	49:33	1.00
Age	63.2 (±8.6)	60.2 (±10.5)	0.03
Hypertension	68 (60.7%)	52 (63.4%)	0.77
Diabetes	34 (30.4%)	18 (22.0%)	0.25
Smoker	10 (8.9%)	6 (7.3%)	0.80
Genotype†			
ε2/ε2	0 (0.0%)	0 (0.0%)	
ε2/ε3	11 (9.8%)	13 (15.9%)	0.21
ε3/ε3	76 (67.9%)	50 (61.0%)	0.32
ε3/ε4	25 (22.3%)	19 (23.2%)	0.89
ε4/ε4	0 (0.0%)	0 (0.0%)	
Carrier†			
ε2 carrier	11 (9.8%)	13 (15.9%)	0.21
ε3 carrier	76 (67.9%)	50 (61.0%)	0.32
ε4 carrier	25 (22.3%)	19 (23.2%)	0.89
Lipid profile‡			
Cholesterol (mg/dL)	196.4 (189.5-203.3)	198.5 (190.4-206.6)	0.70
Triglyceride (mg/dL)	145.3 (129.8-160.7)	161.7 (143.6-179.9)	0.18
HDLc (mg/dL)	41.0 (38.9- 43.0)	44.1 (41.7- 46.5)	0.05
LDLc (mg/dL)	126.4 (120.1-132.6)	122.1 (114.7-129.4)	0.39

*Two sample t-test for continuous variables and chi-square test for nominal variables between the LAA subgroup and the SAO subgroup; †No significant differences in distribution of apoE genotype and apoE carrier between the LAA subgroup and SAO subgroup (χ^2=13.8, 8 d.f., P=0.09 and χ^2=8.4, 4 d.f., P=0.08, respectively); ‡Mean lipid values are adjusted for sex, age, diabetes, hypertension and smoking, with 95% confidence interval in parenthesis.
Abbreviations: LAA, subgroup with atherosclerotic vascular lesion; SAO, subgroup without atherosclerotic vascular lesion.

no significant difference between the LAA (22.3%) and SAO subgroups (23.2%) (P=0.89). Between the LAA and SAO subgroups, no significant differences were found in TC, LDLc, HDLc and TG concentrations. However, adjusted HDLc concentration was lower in the LAA subgroup than in the SAO subgroup, although statistically not significant (P=0.05).

2. The relationship between the apoE genotypes and the serum lipid concentrations

All over the total subjects (N=362), including the ischemic stroke group and the control group, apoE genotype had a significant relationship on LDLc concentration (P=0.01) (Table 3). The ε2 carriers had a significantly lower LDLc concentration than did ε3 and ε4 carriers (P=0.02 and P=0.01, respectively). However, there was no significant difference in LDLc concentration between ε3 and ε4 carriers (P=1.0). Among the control group (N=168), apoE genotype had no significant effect on all four lipid concentrations although the LDLc concentration tended to be lower in ε2 carriers than in ε3 and ε4 carriers. In the SAO subgroup (N=82), the LDLs concentration was significantly different among the 3 genotypes (P=0.01): its concentration was the highest in ε4 carrier followed by ε3 and ε2 carrier in the decreasing order. However, the concentrations of the other lipids (TC, TG, and HDLc) showed no significant difference between different apoE carriers. Among the LAA subgroup (N=112), apoE genotypes had a significant effect only on HDLc: the ε2 carriers had a significantly higher HDLc concentration than did ε3 and ε4 carriers (P=0.02).

DISCUSSION

Many studies have been aimed at characterizing the relationship between apoE polymorphisms and atherosclerosis and ischemic stroke, and it has been postulated that certain apoE alleles (particularly the ε4 allele) are risk factors for the initiation and/or development of atherosclerosis[13, 14]. However, the exact mechanism by which the apoE gene influences atherosclerosis remains unclear, and there is still much controversy over the putative association between ischemic stroke and the ε4 allele. Generally, the ε4 allele has been known to be associated with high TC and LDLc levels[6-12] and the ε4 carriers have been known more likely to develop atherosclerosis[25, 26]. However, the association of the ε4 allele with elevated LDLc levels has not been observed in all studies[15-17]. These inconsistent relationships between apoE and ischemic stroke and between apoE and serum lipid concentrations are probably due to differences in ethnicity, age, and sex distribution in the study group, diagnostic criteria, and environmental factors (e.g., diet, smoking, and drug therapy)[20]. The ethnic and geographical difference is a factor that leads to the inconsistent association between apoE and ischemic stroke. When limited to East Asia, the allele frequencies of ε2, ε3, and ε4 are 3.5%, 85.1%, and 11.2%, respectively, in the Japanese population[9, 27], and are 8.4%, 85.2%, and 6.4%, respectively, in the Chinese population[9, 28]. Age in particular is known to influence apoE allelic frequencies within a population as a confounding factor. Many studies have shown that there is a stronger correlation between ischemic stroke and the apoE ε4

Table 3. The comparison of mean lipid concentrations between apoE carriers in the ischemic stroke group and the control group

	Test	ε2	ε3	ε4	*P**	ε2 vs. ε3	ε2 vs. ε4	ε3 vs. ε4
Total (n=362)	N	44	253	65				
	TC (mg/dL)	191.0 (181.1-200.8)	197.0 (192.9-201.1)	200.7 (192.6-208.7)	0.32	0.80	0.40	1.0
	TG (mg/dL)	171.3 (146.7-195.9)	141.4 (131.2-151.6)	152.9 (132.8-173.0)	0.07	0.09	0.77	0.95
	HDLc (mg/dL)	45.1 (41.7-48.4)	43.4 (42.0-44.8)	41.3 (38.5-44.1)	0.22	1.0	0.28	0.56
	LDLc (mg/dL)	111.6 (102.5-120.8)	125.3 (121.5-129.1)	128.8 (121.3-136.3)	0.01	0.02	0.01	1.0
Control (n=168)	N	20	127	21				
	TC (mg/dL)	186.7 (174.3-199.2)	197.9 (193.0-202.7)	197.9 (185.9-210.0)	0.26	0.31	0.61	1.0
	TG (mg/dL)	167.9 (130.8-205.1)	135.9 (121.3-150.5)	147.4 (111.6-183.2)	0.27	0.35	1.0	1.0
	HDLc (mg/dL)	41.8 (36.6-46.9)	45.1 (43.0-47.1)	42.1 (37.1-47.1)	0.34	0.74	1.0	0.85
	LDLc (mg/dL)	111.3 (99.2-123.5)	125.6 (120.8-130.3)	126.3 (114.6-138.0)	0.09	0.1	0.24	1.0
SAO (n=82)	N	13	50	19				
	TC (mg/dL)	188.0 (167.0-209.0)	195.9 (185.2-206.7)	213.4 (195.7-231.1)	0.14	1.0	0.21	0.31
	TG (mg/dL)	195.6 (141.5-249.7)	158.6 (131.0-186.2)	148.5 (102.9-194.0)	0.38	0.69	0.56	1.0
	HDLc (mg/dL)	46.1 (39.6-52.6)	43.5 (40.2-46.9)	44.8 (39.3-50.2)	0.77	1.0	1.0	1.0
	LDLc (mg/dL)	102.8 (84.6-120.9)	120.7 (111.4-130.0)	139.0 (123.7-154.2)	0.01	0.26	0.01	0.15
LAA (n=112)	N	11	76	25				
	TC (mg/dL)	200.3 (178.0-222.5)	195.8 (187.3-204.2)	195.8 (180.9-210.7)	0.93	1.0	1.0	1.0
	TG (mg/dL)	148.8 (105.0-192.7)	138.4 (121.9-155.0)	163.2 (133.8-192.5)	0.35	1.0	1.0	0.46
	HDLc (mg/dL)	49.3 (43.1-55.5)	40.5 (38.1-42.8)	38.4 (34.3-42.5)	0.02	0.03	0.01	1.0
	LDLc (mg/dL)	121.2 (100.9-141.6)	127.6 (119.9-135.3)	124.7 (111.1-138.3)	0.82	1.0	1.0	1.0

Mean lipid concentrations were adjusted for sex, age, hypertension, DM, and smoking, with 95% confidence interval in parenthesis.
**P* value by ANCOVA for pairwise comparison between apoE carriers after adjusting sex, age, hypertension, DM, and smoking.
Abbreviations: See Table 1 and 2.

allele in younger populations than in older ones[3, 15, 19, 29].

Although there was a selection bias of the ischemic stroke group due to the exclusion of patients who died in the acute stage of ischemic stroke, our study revealed that the distribution of apoE genotypes was significantly different between the ischemic stroke group and the control group. The genotype ε3/ε4 and the ε4 carriers were significantly more frequent (P<0.05) in the ischemic stroke group than in the control group. However, there were no differences in the distribution of apoE genotypes (or apoE carriers) between the LAA and SAO subgroups with different pathogenesis of ischemic stroke. In addition, the ischemic stroke group had a higher LDLc concentration than the control group, but there were no differences in LDLc concentration between the LAA subgroup with atherosclerotic lesion and the SAO subgroup without atherosclerotic lesion. Besides, our study showed that the ε2 carriers had a lower LDLc concentration than ε3 and ε4 alleles, but did not show that the ε4 carriers had a higher LDLc concentration than ε3 allele. These findings are consistent with the study of Shin et al.[30] performed on general population (not on ischemic stroke patients). These findings suggest that although there was an apparent association between the ε4 allele and ischemic stroke and between the LDLc concentration and ischemic stroke, the ε4 allele may have other effects on ischemic stroke that are independent of atherosclerosis due to a high lipid concentration.

Though the serum lipid concentrations used in this study were not always representative values to reflect the basic status of the subjects because there was no consideration of confounding effect such as lipid-lowering therapy and relatively small sample size of the ε4 carriers, it can be postulated that the ε4 allele has no effect on serum lipid concentrations. Therefore, we can postulate other possibilities as to how apoE is involved in the development of ischemic stroke. First, apoE is a factor that is produced in response to neural injury and repair and may influence ischemic stroke by increasing susceptibility to brain injury or by impairing repair mechanisms associated with the presence of the ε4 allele[18]. Second, the apoE genotype may influence the inflammatory response and modulate the risk of acute events by influencing plaque progression and rupture[20].

Because of the complex and multifactorial nature of ischemic stroke, the effect of single apoE polymorphisms on the risk of stroke may be weak when analyzed individually and may result in a false association between apoE and ischemic stroke. Therefore, when evaluating the

impact of apoE or any other genetic factors on the development of ischemic stroke, ethnicity and age, as well as specific conventional risk factors and other genetic factors need to be considered.

In summary, our case-control study, consisting of well-classified patients with ischemic stroke and age-matched controls, demonstrated that there was no difference in the frequency of the apoE genotype $\varepsilon3/\varepsilon4$ (or $\varepsilon4$ carriers) and in serum lipid concentrations between the LAA and SAO subgroups with different pathogenetic origins. Considering that ischemic stroke is a complex and multifactorial disease, the specific gene-environment and gene-gene interactions should also be considered when using specific genetic factors to predict the risk of ischemic stroke.

요 약

배경 : Apolipoprotein E (apoE) 다형성은 혈중 지질 농도 및 죽상경화증의 발생에 관련이 있는 것으로 알려져 있으나 아직까지 이들의 관련성은 확정적이지 못한 상태이다. 본 연구는 case-control study를 통해 한국인에서 혈관내 죽상경화 병변이 있는 허혈성 뇌중풍 환자군(large artery atherosclerosis, LAA군)과 병변이 없는 환자군(small artery occlusion, SAO군)에서 apoE 다형성을 비교하여 apoE 다형성과 이들 환자군에서 혈중 지질 농도와의 관련성을 보고자 하였다.

대상 및 방법 : LAA군 환자 112명과 SAO군 환자 82명으로 구성된 총 194명의 허혈성 뇌중풍 환자군과 168명의 age-matching 건강인으로 구성된 정상군을 대상으로 혈중 지질 농도를 측정하였고, LightCycler (Roche Diagnostics, Mannheim, Germany)를 이용한 실시간 중합효소반응 및 melting curve 분석으로 apoE 유전형을 결정하였다.

결과 : ApoE $\varepsilon4$군의 빈도는 정상군(11.9%)보다 허혈성 뇌중풍 환자군(22.7%)에서 의미 있게 높았으나($P=0.01$), LAA군과 SAO군 간에는 차이가 없었다(각각 22.3% 및 23.2%, $P=0.89$). 저비중 지단백(low density lipoprotein cholesterol, LDLc) 농도는 정상군보다 허혈성 뇌중풍 환자군에서 의미 있게 높았으나($P=0.04$), LAA군과 SAO군 간에는 모든 지질 농도에 차이가 없는 것으로 나타났다. $\varepsilon2$군에서 $\varepsilon3$ 또는 $\varepsilon4$군보다 낮은 LDLc 농도를 나타냈고, $\varepsilon3$군과 $\varepsilon4$군 간에는 LDLc 농도에는 차이가 없었다.

결론 : 비록 한국인에서 허혈성 뇌중풍의 발생과 apoE $\varepsilon4$ 및 LDLc 농도 간에 관련이 있으나, LAA군과 SAO군 간에 지질 농도 및 apoE 유전형의 분포에 의미 있는 차이를 보이지 않았다. ApoE $\varepsilon4$는 허혈성 뇌중풍의 발생과 관련이 있으며 혈중 지질 농도의 이상에 의한 죽상경화증의 발생과는 다른 기전에 의한 위험인자로 생각된다.

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