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Original article

A frameshift deletion mutation in the cardiac myosin-binding protein C gene associated with dilated phase of hypertrophic cardiomyopathy and dilated cardiomyopathy

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KEYWORDS
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Summary
Objectives: A few studies reported that some mutations in the cardiac myosin-binding protein C (MyBPC) gene were associated with dilated phase of hypertrophic cardiomyopathy (D-HCM) resembling dilated cardiomyopathy (DCM). We studied 5 unrelated cardiomyopathy probands caused by an identical mutation in the MyBPC gene. The results of clinical and genetic investigations in these patients are presented in this paper.
Methods: We analyzed MyBPC gene in DCM patients as well as patients with HCM.
Results: An R945fs/105 mutation, 2-base deletion at nucleotides 18,535 and 18,536, was identified in 4 of the 176 HCM probands and in 1 of the 54 DCM probands. Genetic analysis in relatives of those probands revealed another one member with this mutation. A total of 6 subjects had R945fs/105 mutation. The mean age of these six patients at diagnosis was 61 years. At initial evaluation, three of them were diagnosed as having HCM with normal left ventricular (LV) systolic function. The other two patients already had D-HCM. The remaining one patient was diagnosed as having DCM because of reduced LV systolic function (ejection fraction = 31%) without increased LV wall thickness. During follow-up (7.6 years), all three patients with impaired LV systolic function were admitted for treatment of heart failure and/or sustained ventricular tachycardia. Finally, one patient with the diagnosis of D-HCM died of heart failure.
Conclusions: The patients with this mutation may develop LV systolic dysfunction and suffer from cardiovascular events through mid-life and beyond.
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Table 1 Clinical characteristics of patients with an R945fs/105 mutation in the MyBPC gene at intial evaluation.

Patient No.	Gender	Age (years) at initial	Age (years) at diagnosis	Reason for diagnosis	Rhythm	Proven familial HCM	NYHA class
H108	F	79	78	ECG abnormality	SR	−	II
H180	M	59	59	Chest pain	SR	−	I
H053-III-3	F	55	55	ECG abnormality	SR	+	I
H053-III-4	M	50	48	Heart failure	SR	+	III
H085	F	63	63	Heart failure	SR	+	III
D025	M	62	62	Heart failure	AF	−	IV

MyBPC, cardiac myosin-binding protein C; HCM, hypertrophic cardiomyopathy; NYHA, New York Heart Association functional class; F, female; M, male; ECG, electrocardiography; SR, sinus rhythm; AF, atrial fibrillation.

Introduction

Hypertrophic cardiomyopathy (HCM) is a primary myocardial disorder with heterogeneous morphologic, functional, and clinical features [1—4]. Molecular genetic studies have revealed that HCM is caused by mutations in more than 10 genes that encode sarcomere contractile proteins [5—9]. Cardiac myosin-binding protein C (MyBPC) is one of these sarcomere proteins, and mutations in the MyBPC gene have been reported to be associated with delayed expression of hypertrophy and a relatively good prognosis [10—15].

On the other hand, we recently reported that patients with one mutation in the MyBPC gene evolved into dilated phase of HCM (D-HCM) characterized by left ventricular (LV) systolic dysfunction and cavity dilatation, resembling the morphologic features of dilated cardiomyopathy (DCM) [16]. This suggests that patients with MyBPC mutations may at times be diagnosed clinically as having DCM. Therefore, we analyzed the MyBPC gene in DCM patients as well as patients with HCM and had the opportunity to study 4 unrelated HCM families and 1 DCM proband living in Kochi Prefecture, Japan, who were found to have an identical frameshift mutation in the MyBPC gene: a 2-base deletion of a cytosine and guanine at nucleotides 18,535 and 18,536 (R945fs/105). The results of clinical and genetic investigations in these patients are presented in this paper.

Methods

Subjects

The subjects were 176 probands with HCM and 54 probands with DCM. All probands were evaluated at the Kochi Medical School Hospital for confirmation of diagnosis, risk assessment, and symptom management between 1982 and 2007. The diagnosis of HCM was based on echocardiographic demonstration of an unexplained LV hypertrophy (LVH), i.e., maximum LV wall thickness (MLVWT) $\geq$15 mm. The diagnostic criteria of DCM were: (1) a dilated left ventricle [LV end-diastolic diameter (LVEDD) >55 mm)] with ejection fraction (EF) <50% and (2) exclusion of patients with acute myocarditis, specific heart muscle disease, general systemic disease, significant coronary artery stenosis (defined as diameter narrowing of $\geq$50% in any major coronary arteries or their branches), valvular disease, sensitivity/toxic reactions, and history of excessive alcohol intake [17]. Relatives of probands were contacted by the probands themselves and visited our clinic of their own free will. Following the identification of an R945fs/105 mutation, pedigree analysis, including both clinical evaluation and genotyping, was performed. Informed consent was given from all subjects in accordance with the guidelines of the Ethics Committee on Medical Research of Kochi Medical School.

Clinical evaluation

Evaluation of probands and relatives included medical history, clinical examination, 12-lead electrocardiography (ECG), M-mode, two-dimensional (2D) and Doppler echocardiography, and ambulatory 24-h Holter ECG analysis. The severity and distribution of LVH were assessed in the parasternal short axis plane at mitral valve and papilliary muscle levels [18,19]. MLVWT was defined as the greatest thickness in any single segment. LVEDD and LV end-systolic diameter (LVESD) were measured from M-mode and 2D images obtained from parasternal long-axis views, and fractional shortening ($FS = 100 \times (LVEDD - LVESD)/LVEDD$) was calculated. Global EF was determined from apical two- and four-chamber views. LV outflow tract gradient was calculated from continuous-wave Doppler using the simplified Bernoulli equation.

D-HCM was defined as LV systolic dysfunction of global EF <50% at study entry or during follow-up in the presence of (1) an unexplained LV hypertrophy (MLVWT $\geq$15 mm), or (2) previous documentation of unexplained LVH on echocardiography (MLVWT $\geq$15 mm), or (3) proven familial HCM with at least 1 relative who had an unequivocal diagnosis. Concomitant coronary artery disease was excluded by coronary angiography.

Phenotypically affected relatives were defined by the following criteria: (1) MLVWT $\geq$13 mm, (2) presence of major abnormalities on an ECG (i.e. Q wave $\geq$0.04 s in duration or one-fourth of the ensuing R wave in depth in at least two leads, significant ST-T changes, and Romhilt-Estes score >4), or (3) a combination of criteria 1 and 2.

Data regarding survival and clinical status of patients were collected during serial clinic visits. Evaluation of the phenotype was completed before determination of the genotype. Three modes of HCM-related death were defined: (1) sudden and unexpected death (including resuscitated cardiac arrest), in which collapse occurred in the absence or <1 h from the onset of symptoms in patients who previously experienced a relatively stable or uneventful course;

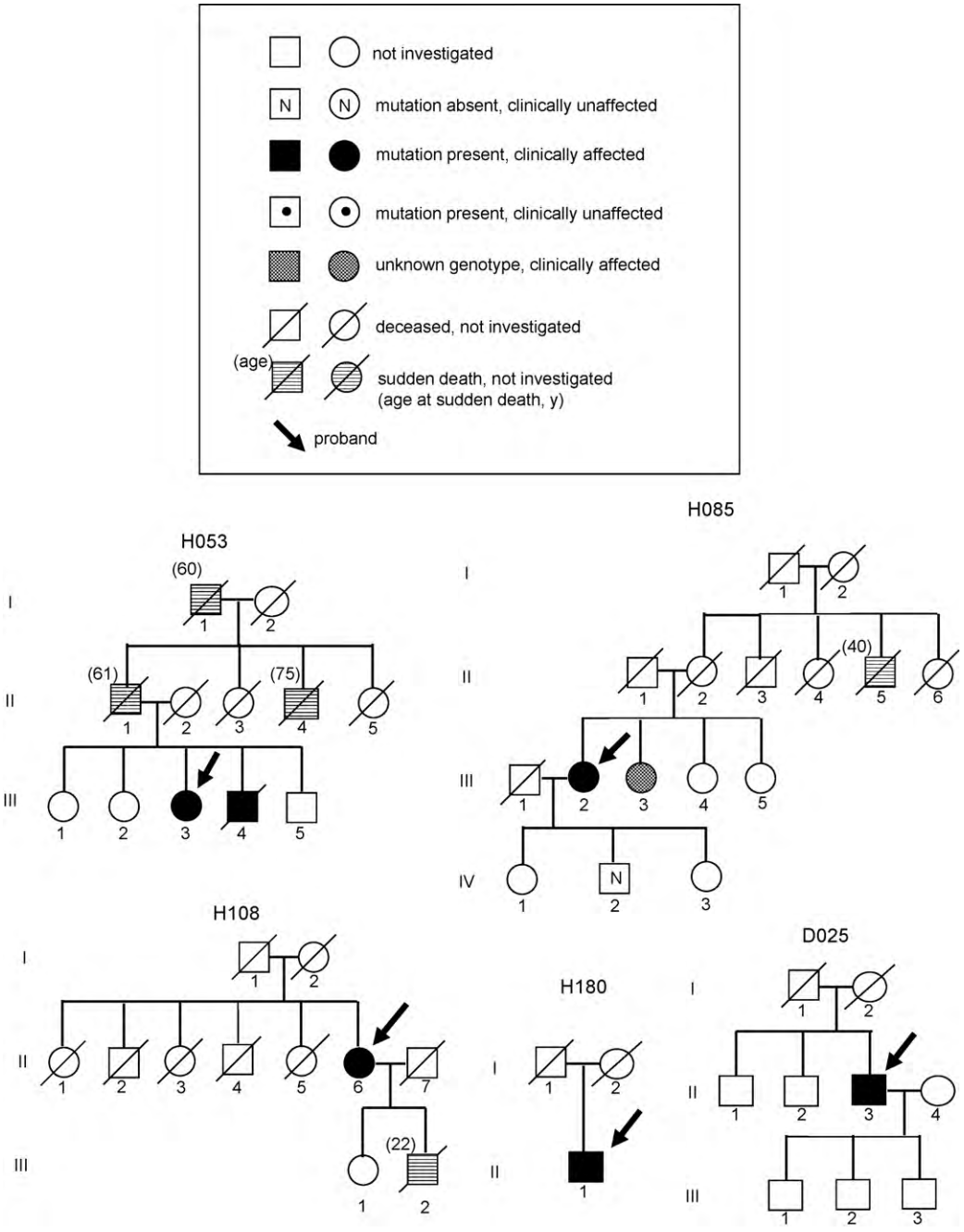

Figure 1 Pedigree of families H053, H085, H108, H180, and D025. The genotypic status and phenotypic status of subjects are indicated.

(2) heart failure-related death, which was in the context of progressive cardiac decompensation ≥1 year before death, particularly if complicated by pulmonary edema or evolution to the end-stage phase; and (3) stroke-related death, which occurred in patients who died as a result of embolic stroke.

Genetic analysis

Peripheral blood samples were taken at the time of clinical evaluation, and they were frozen and stored at −20 °C. Deoxyribonucleic acid (DNA) was extracted using a DNA purification kit from QIAGEN Inc. (no. 51104; Hilden, Germany). In vitro amplification of genomic DNA was performed using the polymerase chain reaction (PCR). Oligonucleotide primers were used to amplify exon 27 of the MyBPC gene. Information on primer sequences and PCR conditions is available upon request. Sequencing was performed using a BigDye Terminator Cycle Sequencing Kit from Applied Biosystems Inc. (no. 4336774; Foster City, CA, USA). The sequences were analyzed on an Applied Biosystems PRISM 3100-Avant Genetic Analyzer in accordance with the manual of the manufacturer. In patients in whom the mutation was iden-

Table 2 Echocardiographic and electrocardiographic characteristics of patients with an R945fs/105 in the MyBPC gene at initial evaluation.

Patient No.	IVS (mm)	PW (mm)	MLVWT (mm)	LVEDD (%)	Global EF (%)	LA (mm)	E/A (m/s/m/s)	QRS width (s)	Abnormal Q wave	ST-T change	GNT	R-E score
H108	17	12	17	40	74	41	0.77/0.80	0.08	+	+	−	2
H180	23	14	25	43	64	39	0.87/0.59	0.14[a]	−	+	+	6
H053-III-3	19	9	19	30	87	31	NA/NA	0.08	−	+	−	2
H053-III-4	14	15	15	52	41	39	0.64/0.27	0.10	−	+	−	5
H085	12	12	15	63	43	47	0.59/0.68	0.12[a]	−	−	−	4
D025	11	10	11	60	31	55	0.90/	0.12	−	+	−	3

MyBPC, cardiac myosin-binding protein C; IVS, interventricular septum thickness; PW, posterior wall thickness; MLVWT, maximum left ventricular wall thickness; LVEDD, left ventricular end-diastolic diameter; EF, ejection fraction; LA, left atrial diameter; E/A, peak E-wave velocity and peak A-wave velocity on trans-mitral Doppler indices; GNT, giant negative T waves (defined as a depth of ≥10 mm); R–E score, Romhilt–Estes score; NA, not available.

[a] Complete right bundle branch block.

tified, confirmation was obtained by re-analysis with direct sequencing from a second blood sample.

To investigate if families carrying the identical mutation were related, haplotype analysis was performed using microsatellite markers defining the MyBPC gene locus. Markers MyBPC3-CA, D11S1784, and D11S1326, flanking the MyBPC gene, were used. To describe haplotype results, the length (base pairs) of allele was put in parentheses after each marker.

Results

Genetic results

An R945fs/105 mutation, a frameshift mutation that causes truncation of cardiac MyBPC protein, was identified in 4 of the 176 HCM probands and in 1 of the 54 DCM probands. Genetic analysis in relatives of those probands revealed another one member with this mutation. A total of 6 subjects, including 5 probands, had an R945fs/105 mutation in the MyBPC gene (Fig. 1). This mutation was thought to be disease-causing based on presence of the mutation in all affected individuals and absence of sequence variation in at least 776 chromosomes from healthy individuals.

Haplotype analysis with highly polymorphic markers was performed in these families to investigate whether an R945fs/105 mutation was likely to have arisen from a common ancestor (founder effect). We found that a unique haplotype, MyBPC3-CA (286) — D11S1784 (144) — D11S1326 (247), was linked to the R945fs/105 mutation in all 5 families, indicating that a common founder of the mutation was likely in these families.

Clinical manifestation

Clinical evaluation was performed and all 6 subjects with an R945fs/105 mutation were found to be phenotype-positive. The clinical characteristics of these six patients at presentation are summarized in Tables 1 and 2. At initial evaluation, three of them (Fig. 1: H108, H180, and H053-III-3) were diagnosed as having HCM with normal LV systolic function. The other two patients (Fig. 1: H053-III-4 and H085) already had D-HCM. The remaining one patient (D025) was diagnosed as having DCM because of LV enlargement and reduced LV systolic function in the absence of increased wall thickness in any LV segment. H108 was diagnosed at the age of 78 years because of ECG abnormality. She did not present LV outflow tract obstruction at initial evaluation in our hospital after commencement of treatment with a beta blocker and disopyramide for LV outflow tract gradient of 138 mmHg by a previous physician. H180 was referred for chest pain at the age of 59 years and had a classic form of HCM. The proband of family H053, individual III-3, was seen due to abnormal ECG without any cardiac symptoms at 55 years of age. She had asymmetric LV hypertrophy. Her brother, H053-III-4, who had symptoms of heart failure (New York Heart Association III), was diagnosed as having D-HCM at the age of 48 years. An echocardiographic study showed mildly increased wall thickness (MLVWT = 15 mm) with diffuse hypokinesis of LV wall motion. The global EF was 41%. H085 complained of shortness of breath and had a LV enlargement with moder-

Table 3 Clinical course of patients with an R945fs/105 mutation in the MyBPC gene during follow-up.

Patient No.	Gender	Age (years) at initial	Rhythm change	NYHA change	Stroke	Hospitalization for heart failure, age (years)	ICD implantation	Status, age (years)
H108	F	79	SR → SR	II → II	–	–	–	Alive, 82
H180	M	59	SR → SR	I → I	–	–	–	Alive, 60
H053-III-3	F	55	SR → SR	I → II	–	–	–	Alive, 73
H053-III-4	M	50	SR → AF	III → IV	–	+, 62	+	Heart failure death, 62
H085	F	63	SR → AF	III → III	–	+, 67	–	Alive, 71
D025	M	62	AF → AF	IV → II	–	–	+	Alive, 65

MyBPC, cardiac myosin-binding protein C; NYHA, New York Heart Association functional class; ICD, implantable cardioverter defibrillator; F, female; M, male; SR, sinus rhythm; AF, atrial fibrillation.

ately reduced LV systolic function. She was referred to our hospital for confirmation of diagnosis of DCM and symptom management. However, detailed observation of the morphology assessed by echocardiography showed that she had a thickened LV wall in some segments with MLVWT of 15 mm. In addition, we were able to obtain clinical information on her younger sister (Fig. 1: H085-III-3), who had been diagnosed at another hospital as having classic HCM with asymmetric LV hypertrophy and normal LV systolic function. Therefore, we diagnosed the proband of family H085, individual III-2, as having D-HCM. D025 was admitted for treatment of heart failure at the age of 62 years. Echocardiography showed LV enlargement and moderately reduced LV systolic function without significantly increased LV wall thickness in any segment (MLVWT = 11 mm). Myocardial biopsy showed no significant myocardial disarray. We diagnosed him clinically as having DCM because there was no previous medical record anywhere and his relatives were not available for investigation.

Regarding a family history of sudden death, there were five relatives from three families (Fig. 1: families H053, H085, and H108) who died suddenly. One individual died at 22 years of age and the other four individuals died after 40 years of age.

Clinical course

Table 3 shows the clinical course of six patients with the mutation (R945fs/105). The follow-up period after the first clinical evaluation was 7.6 ± 6.6 (range 1.3—18.0) years. Three patients with normal LV systolic function at initial evaluation (H108, H180, and H053-III-3) retained sinus rhythm without detection of paroxysmal atrial fibrillation (AF) and were not hospitalized for treatment of any cardiac symptoms. Echocardiography showed preserved LV systolic function at the last follow-up in these three patients. On the other hand, all three patients with reduced LV systolic function (H053-III-4, H085, and D025), who were treated for heart failure and/or arrhythmias with diuretics ($n = 3$), angiotensin-converting enzyme inhibitors ($n = 3$), beta blockers ($n = 2$), and amiodarone ($n = 2$), had paroxysmal or chronic atrial fibrillation at the last follow-up. Two patients were admitted for treatment of heart failure. Furthermore, two patients (H053-III-4 and D025) received an implantable cardioverter defibrillator (ICD) for sustained ventricular tachycardia with instability in circulation. One patient (H053-III-4) died of heart failure at the age of 62 years after a 12-year follow-up from the initial diagnosis of 'end-stage' HCM.

Discussion

To date, more than 200 different mutations in different sarcomere genes have been reported in HCM and DCM patients [5—9,20—22]. Cardiac MyBPC is one of the sarcomere proteins, and mutations in the MyBPC gene have been associated with delayed expression of HCM and a favorable prognosis [10—15]. However, we herein presented different clinical profiles of MyBPC gene mutation associated with LV systolic dysfunction including D-HCM and clinically diagnosed DCM.

Clinical manifestation

HCM is a heterogeneous myocardial disorder with a broad spectrum of clinical presentations and morphologic features [3,4,23—25]. Although LV systolic function is supernormal or preserved in most cases of HCM, progression to systolic impairment (this subtype is so-called D-HCM) occurs in about 5—10% of patients when they are followed for a long time [26—29]. In the present study, half of the patients (three of the six patients with R945fs/105 mutation) showed LV systolic dysfunction at the time of diagnosis of cardiomyopathy. Two of these three patients were diagnosed as having D-HCM based on unexplained LVH, i.e., MLVWT $\geq$15 mm and proven familial HCM with at least one relative who had an unequivocal diagnosis. The other patient (D025) was diagnosed clinically as having DCM because there was no documentation of current or previous significantly increased LV wall thickness. There was also no relative who had diagnosis of HCM, although it was possible that the patient might have had LV hypertrophy sufficient for diagnosis of HCM previously.

In the present study, the mean age of patients at diagnosis was 61 $\pm$ 10 years (range, 48—78 years). Onset of the disease seems to be late in life, although two patients with D-HCM probably had greater LV wall hypertrophy with normal LV systolic function in the early phase. Our data are in accordance with previously reported data for MyBPC mutations [12,14,30—33].

Regarding a family history of sudden death, there were five relatives who died suddenly in this study. It is notable that the majority of sudden deaths occurred in subjects more than 40 years of age (80%; 4 of the 5 individuals). Although sudden death in HCM patients occurs most commonly in children and young adults, it needs to be recognized that the risk of sudden death extends across a wide age range through mid-life and beyond [34]. These findings indicate that even middle-aged or older relatives of patients should be evaluated for family screening strategies.

Clinical course and prognosis

During follow-up (7.6 $\pm$ 6.6 years), three patients with normal LV systolic function were clinically stable without any cardiovascular events. On the other hand, all three patients with reduced LV systolic function at presentation were hospitalized for treatment of heart failure and/or ICD implantation for sustained ventricular tachycardia. One patient died of heart failure at the age of 62 years. It is likely that a significant subset of the patients with this mutation will suffer from HCM-related cardiovascular events (heart failure and arrhythmias) later in life. Although the clinical course in patients with this mutation is not malignant from the view point of survival of the mutations, careful management is needed, particularly in middle-aged and older patients.

Genotype/phenotype relations

An R945fs/105 mutation in the MyBPC gene is predicted to result in a truncation of the protein, including loss of titin-binding sites. This mutation was reported previously as a cause of HCM without LV systolic dysfunction [35]. Although this particular mutation has not been associated with LV systolic impairment, several mutations in the MyBPC gene have been shown to be responsible for HCM with LV systolic dysfunction and dilatation or DCM (missense mutation: R820Q, nonsense mutation: Q1012X, and frameshift deletion mutation: V593fs, we altered the name V592fs/8) [16,30,36]. In the case of R820Q mutation in the MyBPC gene, one elderly patient was reported to be diagnosed as having DCM before genetic identification, similar to a case presented in this paper, although the other patients with R820Q mutation were diagnosed as having HCM [30]. We speculate that our DCM patient (D025) might suffer from D-HCM because the other patients carrying the same mutation in this study were diagnosed as having HCM. Also, there was no previous report that mutations in the MyBPC gene were related only to DCM patients. In some cases, it is difficult to clinically distinguish DCM from D-HCM although in patients with D-HCM a hypertrophied LV wall often remains in some segments even regression of LVH is observed in the process of LV remodeling. These findings indicate that patients with clinical diagnosis of DCM may be actually D-HCM from the etiological point of view.

Progression from HCM to D-HCM has also been well demonstrated in patients with cardiac troponin I or troponin T mutations [37,38]. Compared to the phenotypes in patients caused by these mutations, the age group developing D-HCM seemed to be older in patients with the R945fs/105 mutation in the MyBPC gene. The differences in age for developing D-HCM may be explained by the different mutations or different genes.

Limitations

In the present study, not all of the patients with this mutation had LV systolic dysfunction despite the fact that they all had identical mutations. These results suggest the involvement of other genetic and/or environmental factors and underscore the genetic/phenotypic heterogeneity of HCM. Further investigations are needed to clarify these modifying factors.

Conclusions

An R945fs/105 mutation in the MyBPC gene was identified in 4 of 176 probands with HCM and in 1 of 54 DCM probands. Among the total of six patients with the mutation, three patients showed LV systolic dysfunction with cardiac events of heart failure and arrhythmias: two patients had D-HCM and one patient was diagnosed clinically as having DCM. The patients with this mutation may develop LV systolic dysfunction and suffer from cardiovascular events through mid-life and beyond.

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