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Case report

A sudden death case with myotonic dystrophy providing the single gene mutation of the Na pump promoter gene (SCN5A) regarded as the cause of fatal cardiac arrhythmia

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Background : In myotonic dystrophy the sudden death has been caused by fatal cardiac arrhythmia, based on the abnormality of the genes of the Na pump. We experienced an unexplained sudden death case with myotonic dystrophy and studied the abnormality of Na pump gene (SCN5A).

Case report : The case was hospitalized with acute cholecystitis but she was found dead on bed on the next morning. Her medical history included adult-type myotonic dystrophy at 49 y/o, old myocardial infarct treated coronary stent insertion at 57 y/o, local resection for the neuroendocrine tumor of the duodenum at 60 y/o without recurrence. We were not able to identify the cause of death after a dissection. Na pump gene (SCN5A) was studied with formalin-fixed paraffin-embedded specimens by polymerase chain reaction-single strand conformational polymorphism (PCR - SSCP) and single nucleotide polymorphism (SNP) with restriction enzymes. She showed (C/C + T/C) type of SNP of the Na ion pump promoter gene (SCN5A).

Conclusion : (C/C + T/C) type of SNP of the Na ion pump promoter gene (SCN5A) was confirmed, which probably brought on fetal arrhythmia in this case.

Key words : Na pump gene, SCN5A, exon 7, exon 12, exon 18, exon 20, promoter, single nucleotide polymorphism (SNP), T-1062, T-1418, C/C & T/C type, myotonic dystrophy, sudden death, fatal cardiac arrhythmia, polymerase chain reaction-single strand conformational polymorphism (PCR - SSCP)

Introduction

Many unexplained sudden deaths have been genetically studied (1－3). In myotonic dystrophy the sudden death has been caused by fatal cardiac arrhythmia, based on the abnormality of the genes of the Na+ ion pump (4－6). We experienced a unexplained sudden death case with myotonic dystrophy. She showed (C/C + T/C) type of single nucleotide polymorphism (SNP) of the Na ion pump promoter gene (SCN5A), which probably brought on fetal arrhythmia (7－9).

Case report

The case (SN17-009) was hospitalized with acute cholecystitis in 62-year-old, and percutaneous transhepatic biliary drainage (PTGBD) was conducted. On the next morning, she was found dead on bed. Her medical history was as follows : adult-type myotonic dystrophy at 49 y/o, myocardial infarct in anterior wall of left ventricle treated with coronary stent insertion in anterior descending branch at 57 y/o, local resection for the neuroendocrine tumor of the duodenum at 60 y/o without recurrence. We were not able to identify the cause of death in spite of dissection.

Myotonic dystrophy is complicated with a cardiac muscle lesion as well as a skeletal muscle lesion, and fatal cardiac arrhythmia by the abnormality of the Na pump gene is noted (5, 6). Na pump gene SCN5A was studied with deoxyribonucleic acid (DNA) from the formalin-fixed paraffin-embedded materials. SCN5A exon 7, 12－1, 12－2, 18, 20, and promoters around T-1418 and T-1062 were examined by polymerase chain reaction-single strand conformational polymorphism (PCR - SSCP) according to the previous reports (1－3). Single nucleotide polymorphism (SNP) with the restriction endonuclease was examined for promoters around T-1418 and T-1062 (7－9). The PCR amplification of promoters around T-1418 and T-1062 with primers based on Homo sapiens sodium channel voltage-gated type V (SCN5A) gene, promoter region and exons (AY313163) of DNA Data Bank of Japan (DDBJ) : the primers (5'－＃691－710, 3'－＃850－830 ; ＃ : base sequence on AY313163) for T-1418 and (5'－＃1061－1080, 3'－＃1180－1161) for T-1062, respectively (Fig. 1) (7－9). As for the PCR product of promoter T-1418 and T-1062, they were 161 bp and 123 bp, respectively. They were, furthermore, digested with restriction endonuclease Ear I and HaeIII (Takara Co) (Fig. 1). The contents of the enzyme digestion consisted of sample 2μl, H2O 10.9μl, 10xBuffer 1.5μl, and en-

zyme 0.6μl, were incubated at 37 degrees Celsius, 12 hours. The results showed that exon 7, 12－1, 12－2, 18, and 20 were normal. About promoters T-1418 and T-1062, only T-1062 band was found after a restriction enzyme digestion. As a result, the SNP type of promoters T-1418 and T-1062 was（T or C）and C, respectively, probable haploids（C/C+T/C）（Fig. 1－3）（7, 8）.

Conclusion

The case with myotonic dystrophy showed unexplained sudden death. The possibility of fatal arrhythmic frequently complicated in myotonic dystrophy was studied with Na pump SCN5A genes. As a result, SNP（C/C + T/C）type of promoter around T-1418 and T-1062 was found（7, 8）. It was reported that this SNP type was significantly complicated with cardiac arrhythmia, and our case of sudden death was affected with fatal cardiac arrhythmia.

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和　文　抄　録

症例報告

Na ポンプ遺伝子（SCN5A）プロモーター遺伝子の変異による致死性不整脈が突然死の原因と思われる筋強直性ジストロフィー突然死の１症例

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背景：我々は、原因不明の突然死症例の遺伝子学的に原因追求してきた。成人型強直性筋ジストロフィー症例には突然死が多く、致死性不整脈が原因と考えられている。また、Na＋イオンポンプの遺伝子異常が指摘されている。今回、成人型筋ジストロファイーの原因不明の突然死を経験し、Na イオンポンプ遺伝子 SCN5A に関して検討した。

症例内容：62才の女性で、急性胆嚢炎で入院し、Percutaneous transhepatic biliary drainage（PTGBD）が施行された（SN17－009）。翌朝、死因不明の突然死で発見された。既往歴は、49才に成人型筋強直性ジストロフィー、57才に心筋梗塞でステント挿入、60才に十二指腸の神経内分泌腫瘍で局所切除術を受けた。解剖にもかかわらず死因を特定できなかった。Na ポンプ SCN5A 遺伝子検査を実施した。プロモーターの一塩基多型（single nucleotide polymorphism, SNP）による（C/C + T/C）型が認められた。

結論：Na ポンプ SCN5A 遺伝子検査により、プロモーターの一塩基多型（SNP）上、（C/C + T/C）型が認められ、致死的不整脈が示唆された。

キーワード：Na ポンプ遺伝子、SCN5A、exon7, 12, 18, 20, プロモーター、１塩基多型、T-1062、T-1418、C/C & T/C 型、筋強直性ジストロフィー、突然死、致死性不整脈、ポリメラーゼ連鎖反応、一本鎖高次構造多型、ホルマリン固定―パラフィン包埋検体

promoter		T-1418	T-1062	
primer	5'-	#691-710	#1061-1080	
	3'-	#850-831	#1180-1161	
PCR product		161bp	123bp	
restriction enzyme		Ear I	Hae III	
	target bases	ctctT/ca	gg/Cc	
	normal type	ctctT/ca	ggTc	
type of haploid	T/T (rest of band)	ctctT/ca (-)	ggTc (+)	most frequently found in normal Japanese (75%)
	C/C	ctctCca (+)	gg/Cc (-)	frequently found in normal Japanese (25%)
	T/C	ctctT/ca (-)	gg/Cc (-)	
	C/T	ctctCca (+)	ggTc (+)	

haploid type: T・C/C pattern suggested conduction abnormality (7, 8)

Fig. 1. Genetic characteristics of promoter T-1418 and T-1062

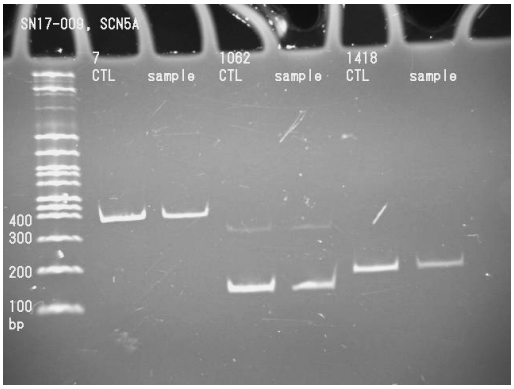

Fig. 2. Electrophoresis of PCR products before treatment by restriction enzyme.
PCR products of exon 7, promoter T-1062, T-1418. CTL : normal control.

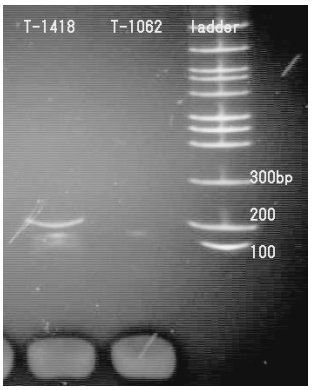

Fig. 3. Posttreatment by enzyme.
PCR product persisted in promoter T-1418, suggested that base of＃1418 was diploid T or haploid T in sequence. PCR product was digested and lost in promoter T-1062, suggested that base of＃1062 was only C.

（2018／01／25受付）