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The necessity of implantable cardioverter defibrillators in patients with Kearns-Sayre syndrome - systematic review of the articles -☆

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ABSTRACT

The most common cardiac feature of Kearns-Sayre syndrome (KSS) is atrioventricular block (AVB), and pacemaker implantations (PMIs) are recommended for KSS patients with advanced AVB. However, some KSS patients develop fatal arrhythmias such as polymorphic ventricular tachycardia (PMVT) and ventricular fibrillation (VF) and die suddenly even after PMIs. We report a patient with KSS who developed PMVT, VF, and QT prolongation, and was treated with mexiletine and successfully managed with an implantable cardioverter defibrillator (ICD). We reviewed the literature on arrhythmias in KSS published from 1975 to 2018. There were 112 patients with arrhythmia-associated KSS, 10 died, and 6 died suddenly after the PMI. The first manifestation of an arrhythmia was bundle branch block, then it progressed to AVB, and developed into complete AVB (CAVB) in about half the KSS patients. Ventricular arrhythmias were documented in 12 patients, and 8 were implanted with defibrillators afterwards. One patient after the implantation of a cardiac resynchronization therapy defibrillator (CRT-D) was treated for VF by an appropriate shock. This fact suggested that VF occurred even under proper pacing, and that defibrillators were effective. Pacemakers may suppress early afterdepolarizations (EADs) associated with a QT prolongation due to bradycardia. Similarly, mexiletine may suppress EADs by blocking the late sodium and Ca currents. Ventricular arrhythmias observed under suppression of EADs may be caused by delayed afterdepolarization (DADs) via an increasing intracellular Ca concentration due to mitochondrial dysfunction. Therefore, a PMI alone may not be sufficient to prevent sudden death, and an ICD implantation should be necessary.

1. Introduction

Kearns-Sayre syndrome (KSS) is a rare disease with a mitochondrial abnormality characterized by progressive extraocular paralysis, retinal pigment degeneration, and cardiac conduction defects. In cases with only extraocular paralysis, it is called chronic progressive external ophthalmoplegia (CPEO), but it is essentially the same disease. Most cases are first noticed by eyelid ptosis in the second decade, then fatigue, muscle weakness, sensorineural deafness follow. Subsequently, cardiac conduction failure progresses gradually. Early epidemiologic studies estimated the minimum population prevalence of mitochondrial disease is between 9.2 and 16.5 per a population of 100,000 [1]. The general characteristics and prognosis of KSS has been reported by Khambatta [2]. The intelligence of KSS was generally within normal, but 31% of KSS patients had a cognitive decline, 77% neurologic weakness, 89% external ophthalmoplegia, 86% ptosis, 14% diabetes mellitus, and 9% hypothyroidism. However, all patients died of sudden cardiac death.

Atrioventricular block (AVB) is the most frequent cause of a cardiac conduction defect in KSS. The AVB of KSS is known to progress rapidly

Abbreviations: KSS, Kearns-Sayre syndrome; AVB, atrioventricular block; CAVB, complete atrioventricular block; PMVT, polymorphic ventricular tachycardia; MMVT, monomorphic tachycardia; VF, ventricular fibrillation; PMI, pacemaker implantation; ICD, implantable cardioverter-defibrillator; SCD, sudden cardiac death; MVP, mitral valve prolapse; MR, mitral valve regurgitation; CPEO, chronic progressive external ophthalmoplegia; AHA, American Heart Association; ACC, American College of Cardiology; HRS, Heart Rhythm Society; ESC, European Society of Cardiology; CLBBB, complete left bundle brunch block; CoQ10, Coenzyme Q10; ICU, intensive care unit; ECG, electrocardiogram; TdP, torsade de pointes; CPA, cardiac pulmonary arrest; DCM, dilated cardiomyopathy; LVNC, left ventricular non-compaction cardiomyopathy; CRBBB, complete right bundle brunch block; ATP, anti-tachycardia pacing; CRT-D, cardiac resynchronization therapy with defibrillator; S-ICD, subcutaneous implantable cardioverter-defibrillator; MELAS, mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes; WPW, Wolff-Parkinson-White; APD, action potential duration; EAD, early afterdepolarization; DAD, delayed afterdepolarization.

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and the main cause of death has been considered to be complete atrioventricular block (CAVB) [3]. Bradycardia has also been reported in KSS, it has been thought to be able to be managed adequately with a permanent pacemaker implantation (PMI). The AHA/ACC/HRS and ESC guidelines recommend a prophylactic PMI for advanced second or third degree atrioventricular block in KSS patients [4,5]. However, some KSS patients develop fatal arrhythmias such as polymorphic ventricular tachycardia (PMVT) and ventricular fibrillation (VF), even after a PMI, and die suddenly even after the PMI. However, only a few reports have introduced implantable cardioverter-defibrillator (ICD) in patients with KSS. The incidence of such fatal arrhythmias and sudden cardiac death (SCD) remains unknown, and it is unclear how much benefit is gained by an ICD [6]. Further, there are no recommendations for ICDs for KSS in the guidelines. We experienced a KSS patient who had a PMVT and VF, and was successfully managed by an ICD implantation. We also reviewed the incidence of fatal arrhythmias and SCD and clarified the necessity of an ICD in patients with KSS.

2. Methods

An electronic literature search of Medline in addition to a hand-search of reference lists for published data was carried out. The search terms included "KSS (or Kearns Sayre syndrome)" and "arrhythmia (or "block" or "tachycardia" or "tachyarrhythmia")". The studies published from 1975 to 2018 were reviewed. The search was limited to English language studies only. Further, the studies that were not available on the internet were excluded. There were 112 arrhythmia-associated KSS patients included in 59 available English articles that have been reported so far along with our patient.

3. Clinical case

Ptosis, external ophthalmoplegia, and hyperuricemia appeared since she was 12 years old, and she was followed for chronic progressive external ophthalmoplegia (CPEO). Complete left bundle branch block (CLBBB) developed when she was 14 years old and progressed to second degree atrioventricular block from 16 years old, and she was diagnosed with Kearns-Sayre syndrome (KSS). There was no family history of mitochondrial disease, cardiac disease, or sudden death. She had been taking fursultiamine, CoQ10, and carnitine. She was referred to our department when she was 18 years old for an examination of her arrhythmia (Fig. 1A), and she was followed up in the outpatient clinic afterwards. The ECG at her regular medical examination 2 weeks before admission showed CAVB (Fig. 1B).

When she was 19 years old, she was transferred to our emergency room following two episodes of syncope in her school and at home. Her syncopal episodes were described as a sudden faintness while she was sitting in a chair and going up the stairs. Cardiopulmonary

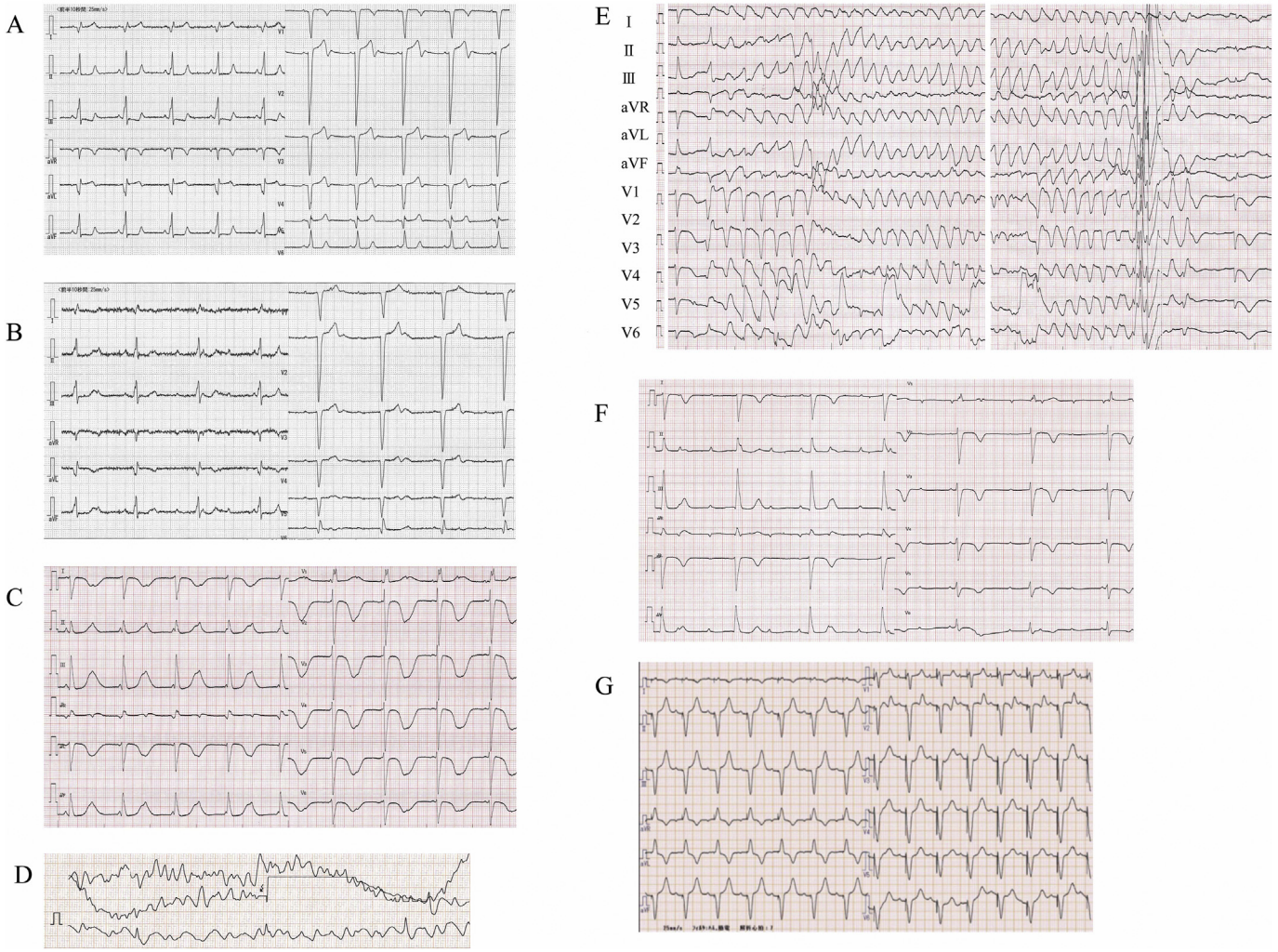

Fig. 1. Electrocardiogram in the patient. A. ECG when she was 18 years old. CLBBB and mild prolongation of the QTc (460 ms). B. ECG 2 weeks before the CPA. CAVB and moderate prolongation of the QTc (500 ms). C. Initial ECG in our emergency department. CRBBB and severe prolongation of the QTc (690 ms). D. ECG during observation in the emergency department. VF developed and she returned to sinus rhythm after a DC shock. E. ECG in our ICU. TdP initiation and spontaneous termination in about 10 s without any trigger events. F. ECG after magnesium sulfate and mexiletine. CAVB continued but the QTc shortened to 490 ms. G. ECG after the ICD implantation. The base rate was 60 bpm and upper tracking rate 130 bpm. Although there was atrial pacing and ventricular sensing, the QTc interval remained at 570 ms.

resuscitation was performed by bystanders because she was pulseless, and she recovered within 3 min. When she arrived at our institute, her consciousness was E3V4M5 on the Glasgow coma scale. Her heart rate was 50 bpm and she was in a ventricular escaped rhythm, and her blood pressure was 105/59 mmHg, heart sounds were regular, and she had no murmur. The QTc (Bazett) interval was prolonged to 690 ms (Fig. 1C). In the blood gas analysis, metabolic acidosis was observed. The potassium and magnesium were within normal range. Suddenly a sustained ventricular tachycardia at 220 bpm appeared in the emergency room, resulting in ventricular fibrillation (VF) (Fig. 1D). Electrical defibrillation with 150 J successfully terminated her VF, and she recovered to sinus rhythm. She was admitted to the ICU for emergent care.

After hospitalization, she suddenly developed torsade de pointes (TdP), but it spontaneously terminated in 10 s (Fig. 1E). Mexiletine, magnesium sulfate, and potassium chloride were effective for suppression the VF and TdP, but an electrocardiogram showed complete atrioventricular block with a ventricular escape rate of 39 bpm. The QTc interval shortened to 490 msec (Fig. 1F). Those arrhythmias were thought to be due to KSS, and we performed an ICD implantation (Boston Scientific, Dynagen EL ICD DR) for secondary prevention on the third day of hospitalization. The atrial lead was an Ingevity MRI lead, and the ventricular lead was a Reliance 4-front.

During the implantation of the ICD, most of her right atrium had a low voltage, and only a few sites where sufficient to pace. The atrial leads were screwed into the lower right atrial appendage and the ventricular leads were screwed into the apex of the right ventricle. The resistance was 732 Ω in the right atrium and 484 Ω in the right ventricle. The sensing voltage of the atrial lead was 5.4 mV, but because of CAVB, we could not measure the sensing voltage of the ventricular lead. The pacing mode was DDD, the basic rate of the ICD was set to 60 bpm, and the upper tracking rate was 130 bpm. The pacing threshold was 0.7 V/0.4 ms in the atrium and 0.4 V/0.4 ms in the ventricle. The output was set to 2.5 V/0.4 ms in the right atrium, and 2.5 V/0.4 ms in the right ventricle. Anti-tachycardia pacing (ATP) was set to perform at 160 bpm or more and we set a shock of 10 J after the ATP of 180 bpm or more. We set a shock of 41 J for VF above 220 bpm.

After the ICD implantation, her heart rate became 60–130 bpm with A sensing and V pacing. Her activity and quality of life markedly improved after the ICD implantation. She was discharged without any antiarrhythmic medications on the 12th postoperative day after discharge from rehabilitation. She has not developed any ventricular arrhythmias during 9 months of follow up.

4. Literature review

4.1. Characteristics and symptoms

Arrhythmia-associated KSS has been reported in 112 patients (66 males, 43 females, 3 unknown) in 59 available English articles from 1975 to 2018. The median age of the initial neuromuscular symptoms was 11 years old (0–40 years old), and the median age of the first arrhythmia detection was 15 years old (7–65 years old). In those patients, 10 patients died, and 6 patients died suddenly after a PMI in their teens [7–12] (Table 1). None of them had any history of syncope, cardiac arrest, or QT prolongation prior to the sudden death. Two of them reported a QTc interval, which was 420 ms and 474 ms respectively. Between those patients, 28 (25.0%) experienced syncope, 13 (11.6%) experienced cardiopulmonary arrest (CPA), 19 (17.0%) progressed to chronic heart failure due to dilated cardiomyopathy (DCM) or left ventricular non-compaction cardiomyopathy (LVNC) [3,7,12–21] (Table 1).

4.2. Arrhythmias and device implantations

There were 49 complete AVB patients, 6 second-degree AVB, 2 first-degree AVB, 7 right bundle branch block, 1 left bundle branch block, 1 tri-fascicular block, 6 bi-fascicular block, 2 single fascicular block, 2 sick sinus syndrome (SSS), 9 PMVT, 5 MMVT, and 3 VF in our review (Table 1). In many patients, the first manifestation of an arrhythmia was bundle branch block, then it progressed to the atrioventricular block, and the block often developed into a more severe type atrioventricular block. Ventricular arrhythmias were documented in 12 patients (10 females, 2 males), and 7 of them were implanted with an ICD or CRT-D afterwards, and all survived [1,12,13,22–28]. Pacemakers were implanted in 67 patients, ICDs in 6 and CRT-Ds in 2. Only 1 patient who was implanted with a CRT-D had any documented appropriate shock therapies for VT, and there were no reports of any inappropriate shock therapies of the ICDs in those references [13]. Four years after the PMI, biventricular dysfunction and non-sustained VT (NSVT) appeared, and the pacemaker was upgraded to a CRT-D. However, one week later VF appeared and the CRT-D worked properly. On the other hand, there have been no reports about inappropriate therapies. Surprisingly, 6 of 67 patients who were implanted with pacemakers had sudden cardiac death a few years after the PMI, even though the pacemaker was working normally. In those 6 patients, 3 had CAVB, 1 had second-degree AVB, and 1 had CRBBB (Fig. 2). The reference No. 8 patient died while waiting for a permanent pacemaker implantation in spite of temporary pacing [8]. The reference No. 9 patient had documented VT that needed cardioversion [9]. We cannot completely deny the possibility of a malfunction of the pacing, but we also completely excluded the chance of sudden death by ventricular arrhythmias. All the patients with documented ventricular arrhythmias survived as a result of an ICD or CRT-D implantation in the medical department. Conversely, patients without a history of ventricular arrhythmias were considered to have died from their first episode at home. All the sudden deaths occurred out of hospital, and none of the reports described the details of the deaths. Some of the devices were implanted prophylactically for patients with RBBB and LBBB. Sudden death was observed even in a patient with RBBB [8] (Fig. 2).

Table 1

Feature	No of patients (%) ($N = 112$)
Clinical features	
Male	66 (58.9)
Death	10 (8.9)
CPA	13 (11.6)
Syncope	28 (25.0)
CHF	19 (17.0)
Bradycardia	
CAVB	49 (43.8)
2°AVB	6 (5.4)
1°AVB	2 (1.8)
RBBB	7 (6.3)
LBBB	1 (0.9)
Left FB	2 (1.8)
Tri-FB	1 (0.9)
Bi-FB	6 (5.4)
SSS	2 (1.8)
Tachycardia	
PMVT	9 (8.0)
MMVT	5 (4.5)
VF	3 (2.7)
Device treatment	
PMI	67 (59.8)
ICD	6 (5.4)
CRT-D	2 (1.8)

CPA = cardiac pulmonary arrest, CHF = chronic heart failure, CAVB = complete atrioventricular block, AVB = atrioventricular block, RBBB = right bundle brunch block, LBBB = left bundle brunch block, FB = fascicular block, SSS = sick sinus syndrome, PMVT = polymorphic ventricular tachycardia, MMVT = monomorphic ventricular tachycardia, VF=ventricular fibrillation, PMI = pacemaker implantation, ICD = implantable cardioverter-defibrillator, CRT-D = cardiac resynchronization therapy with defibrillator.

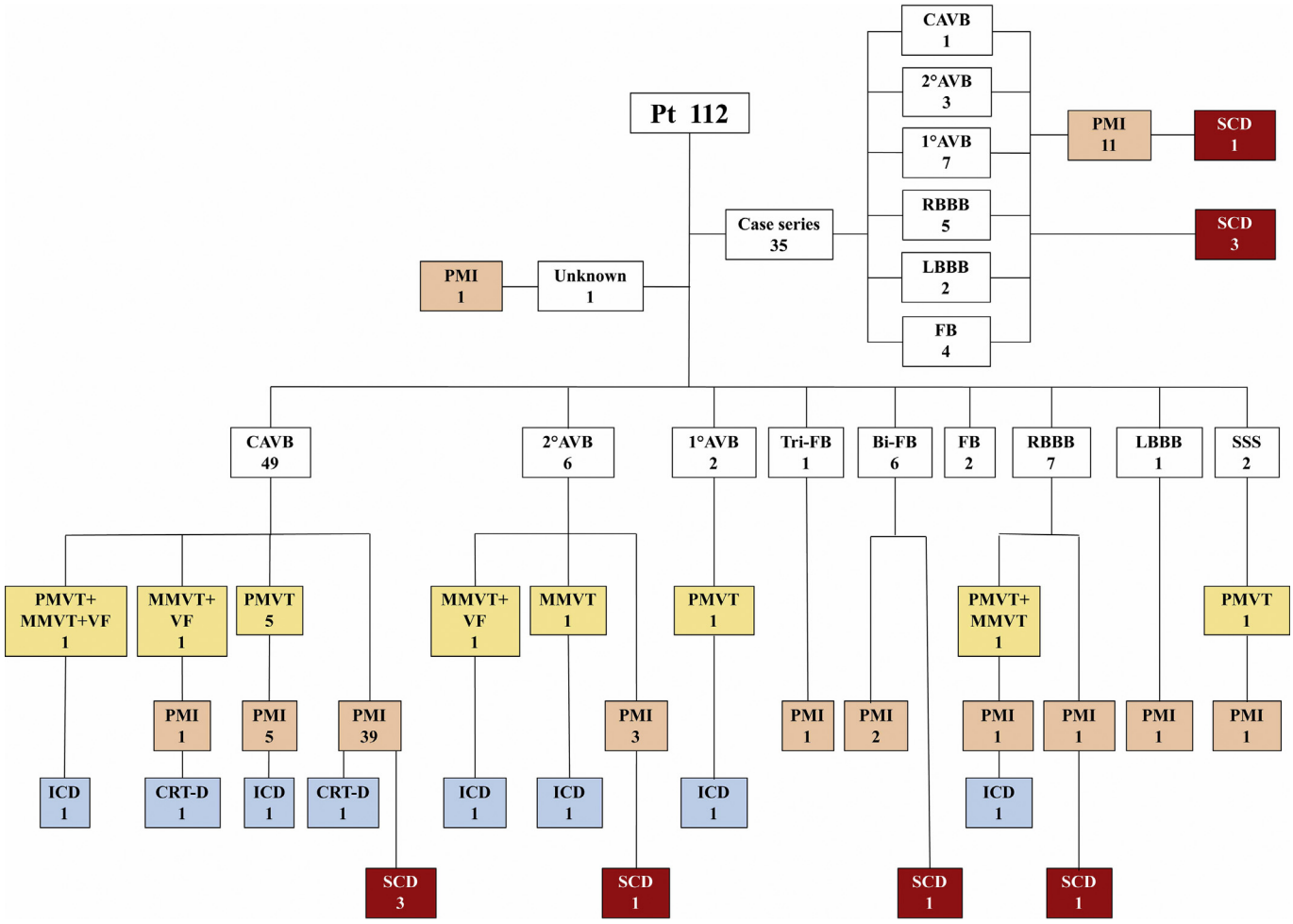

Fig. 2. The association between SCD, arrhythmias, and device treatment. The 10 SCD patients included 6 patients after a PMI. Ventricular arrhythmias were documented in 12 patients, and 8 of them were implanted with an ICD afterwards, and all survived. Because 35 patients were included in the case series, the individual details were unknown.

4.3. QT prolongation

In 12 patients, the QTc (Bazett) time was described, and in 6 the QTc time was more than 500 ms [7,8,12,15,22–25,27–30]. The mean QTc interval (628 ± 91 ms) was significantly more prolonged in 9 PMVT patients (8 females and 1 male, and median age was 33 years old; 14–47 years old) than the patients without PMVT (470 ± 47 ms). All PMVT patients had QT prolongation except for 1 patient [12,22–28]. In those QT prolongation patients, 1 patient was confirmed to have a KCNQ1 mutation [23].

5. Discussion

All 10 patients with KSS died suddenly usually in their teens, and 6 of 10 patients were implanted with a pacemaker before the sudden cardiac death in our study [2,7–11]. This fact suggested that the sudden death in KSS might not be bradycardia due to CAVB, but ventricular arrhythmias such as PMVT, MMVT, or VF. Eight of 12 patients who had documented ventricular arrhythmias were implanted with ICD or CRT-D afterwards, and all of them survived [1,12,13,22–28,31]. They had no QT prolongation and no histories of ventricular arrhythmias. The first ventricular arrhythmia attack may be fatal, even when no bradycardia such as CRBBB is present.

Barackpour reported that the patient who developed non-sustained VT after a PMI were upgraded to a CRT-D [13]. After the implantation of the CRT-D, VF was documented and the patient survived due to an appropriate shock therapy. Therefore, we speculated that some of the sudden death after PMIs may be due to ventricular arrhythmias.

Our study showed that a pacemaker alone was not enough to prevent sudden death in KSS. Although pacemakers have been implanted in about half of the KSS patients, ICDs have been implanted in only 7% [1,12,13,24,25,31]. The AHA/ACC/HRS and ESC guidelines recommend a prophylactic PMI as a class I indication for advanced second or third degree AVB in patients with cardiomyopathy such as KSS [4,5]. But ventricular stimulation by a pacemaker may possibly induce MMVT or VF, and all KSS patients who are implanted with a PMI are at high risk of SCD. They may require an upgrade to an ICD. Although the appropriate time to implant the ICDs is unknown, we recommended that it is desirable to implant ICDs at the timing when some conduction disturbance appears in the KSS patients, because most of the patients died suddenly when only a mild conduction disturbance was documented.

We could not find any reports on catheter ablation of tachyarrhythmias in KSS patients, but there were some reports of the successful catheter ablation of tachyarrhythmias in the patients with other mitochondria disease. It is known that MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes) is often associated with WPW syndrome [32,33], and there are several reports that radiofrequency ablation has been performed for the accessory pathway.

PMVT was seen in 8% of KSS patients. All PMVT patients had QT prolongation except for 1 patient [12,22–28]. The cause of PMVT in KSS remains unknown. Kabunga reviewed 10 patients with PMVT, and they reported that PMVT occurred in the setting of QT prolongation and

bradycardia [1]. On the other hand, Oginosawa reported a 29 year old KSS woman with PMVT and first-degree AVB, whose heart rate was about 70 bpm and QTc 449 msec [24]. They thought that her PMVT was induced by neither bradycardia nor QT prolongation, but by fatty infiltration and fibrosis of the atrioventricular conduction system, and myocyte mitochondrial proliferation. Myocardial degeneration in KSS might lead to QT prolongation and PMVT. Skinner reported a case of KSS overlapping with long QT syndrome due to a KCNQ1 mutation [23]. They thought that a PMI and administration of magnesium for the purpose of increasing the heart rate and shortening the QT duration was considered to be ineffective to prevent sudden death.

We expected to use mexiletine to shorten the QT interval, and actually the QT interval became shorter and could prevent ventricular arrhythmias. Mexiletine blocks the late sodium current (late I_{Na}), and also Ca current (I_{CaL}) [34,35], which may result in shortening the ventricular action potential duration (APD) and QT interval, and also suppress early afterdepolarizations (EADs). In our patient, the ventricular arrhythmias may have been induced by a bradycardia-dependent prolongation of the APD and QT interval, and also by an augmentation of the EADs. Therefore the ventricular arrhythmias may have been suppressed by the increased heart rate due to ventricular pacing, and also could have suppressed the EAD by mexiletine.

It has been reported that some KSS patients develop ventricular arrhythmias without any bradycardia or even after a PMI. Mitochondrias act to keep the intracellular Ca concentration like the sarcoplasmic reticulum. The intracellular Ca concentration may become increased by damaged mitochondria in KSS patients resulting in an increase in the delayed afterdepolarizations (DADs), and also could increase the possibility of ventricular arrhythmias. Mexiletine decreases the intracellular Ca concentration by blocking the I_{CaL}, resulting in the inhibition of DADs and ventricular arrhythmias. Taken together, we considered the triggered activity caused by EADs due to bradycardia and DADs due to mitochondria dysfunction may contribute to the ventricular arrhythmias in KSS patients (Fig. 3).

Hubner reported that about 2–5% of heart muscle cells show an extreme loss of myofibrils and an excessive accumulation of moderately enlarged mitochondria in biopsied cardiac muscle specimens [17]. In the cells of the conduction system, they observed abnormal dense rounded mitochondria with tubular cristae. This finding also suggested that the conduction disturbances of KSS might be caused by a mitochondrial abnormality.

Our patient was documented to have complete left bundle branch block when she was 16 years old, and it progressed to second degree AVB when she was 18 years old, and complete atrioventricular block when she was 19 years old. Only 2 weeks after the documentation of the complete AVB, she developed VF, MMVT, and PMVT. Welzing reported a 9-year-old boy who advanced from a normal electrocardiogram to complete AVB in 10 months [3]. Careful follow-up is necessary because there is a rapid progression of the cardiac conduction defect and fatal arrhythmias in patients with KSS. Since KSS patients usually have cardiac conduction defects, pacing therapy is required in addition to defibrillation therapy.

Generally, KSS patients have been reported to have conduction disturbances, but their cardiac function remains within normal range. However, in our report, 19 of 112 reported patients had heart failure. In those 19 patients, only 2 developed ventricular arrhythmias, consequently ventricular arrhythmias may not be related to the ventricular dysfunction in KSS patients. Most Patients developed heart failure in their twenties, and some needed a heart transplantation due to a rapid progression to dilated cardiomyopathy [36–38]. Wang reported that DCM and AVB were induced by heart-specific inactivation of mitochondrial transcription factor A (*Tfam*) [39]. This report may suggest

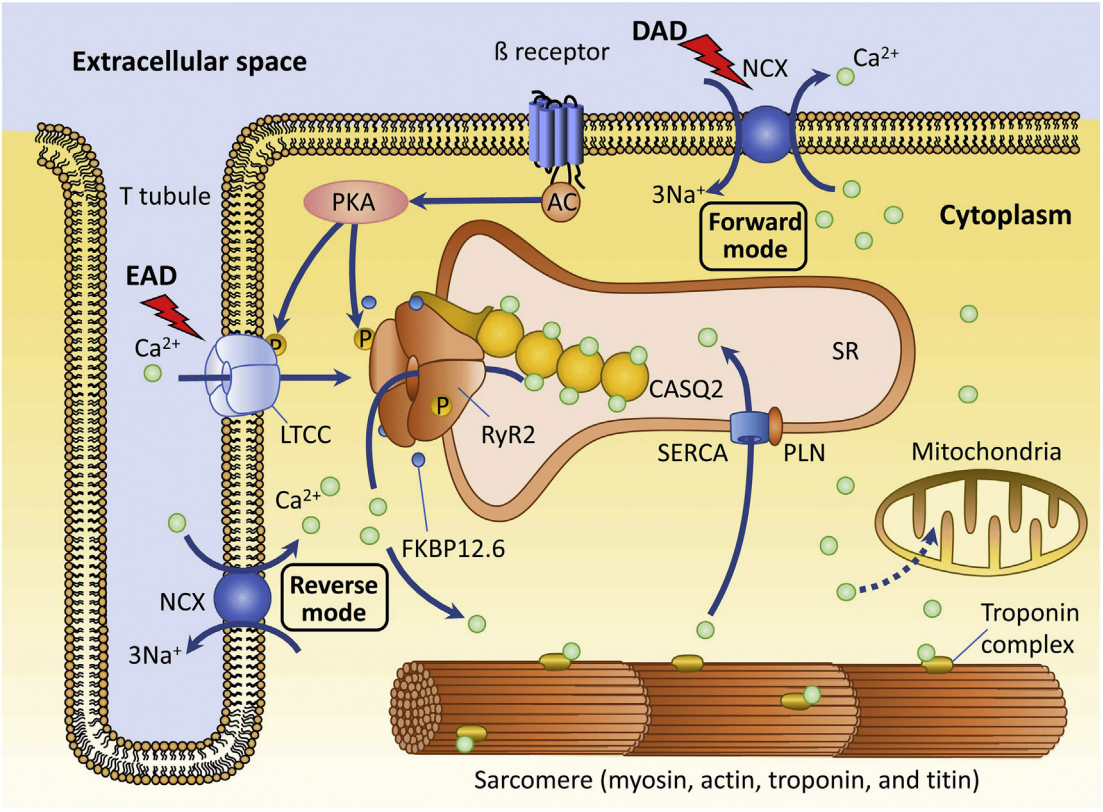

Fig. 3. Calcium handling and possible mechanism of ventricular arrhythmia in patients with KSS. See further discussion in the text. LTCC = L-type voltage-dependent calcium channels; PKA = protein kinase A; FKBP12.6 = calstabin2; CASQ2 = calsequestrin 2; SR = sarcoplastic reticulum; SERCA = sarcoplastic reticulum Ca^{2+}-ATPase; NCX = Na^+/Ca^+ exchanger; AC = adenylate cyclase; EAD = early afterdepolarization; DAD = delayed afterdepolarization.

that mitochondrial abnormalities may also play an important role in the progression of DCM and AVB in KSS patients.

Several limitations of our study need to be considered. Firstly, the papers were only in English and available on the Internet. Secondly, there was a limitation on subjects to KSS patients who have already documented arrhythmia. Therefore, we could not include cases that suddenly died before some arrhythmia was discovered. Thirdly, many papers did not clarify the type of arrhythmia and QT intervals for each patient before sudden death. If detailed data of sudden death cases are available, the necessity of ICD and the optimal implantation time will become clearer. Finally, consideration of the mechanism of ventricular arrhythmias via EADs and DADs should be verified by basic experimentation in the future.

6. Conclusion

Sudden death caused by ventricular arrhythmias is one of the most important issues in patients with KSS. EADs caused by bradycardia and DADs caused by mitochondrial abnormalities may deteriorate into causing life threatening ventricular arrhythmias. Therefore, a PMI alone may not be sufficient to prevent sudden death, and an ICD implantation would be necessary when patients developed bradycardia.

Declarations of interest

None.

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