Short QT syndrome: clinical findings and diagnostic–therapeutic implications

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Aims Clinical presentation, occurrence of sudden infant death, and results of the available therapies in the largest group of patients with short QT syndrome (SQTS), studied so far, are reported.

Methods and results Clinical history, physical examination, electrocardiogram (ECG), exercise stress testing, electrophysiological study, morphological evaluation, genetic analysis and therapy results in 29 patients with SQTS and personal and/or familial history of cardiac arrest are reported. The median age at diagnosis was 30 years (range 4–80). In all subjects, structural heart disease was excluded. Eighteen patients were symptomatic (62%): 10 had cardiac arrest (34%) and in 8 (28%) this was the first clinical presentation. Cardiac arrest had occurred in the first months of life in two patients. Seven patients had syncope (24%); 9 (31%) had palpitations with atrial fibrillation documented even in young subjects. At ECG, patients exhibited a QT interval ≤320 ms and QTc ≤340 ms. Fourteen patients received an implantable cardioverter-defibrillator (ICD) and 10 hydroquinidine prophylaxis. At a median follow-up of 23 months (range 9–49), one patient received an appropriate shock from the ICD; no patient on hydroquinidine had sudden death or syncope.

Conclusion SQTS carries a high risk of sudden death and may be a cause of death in early infancy. ICD is the first choice therapy; hydroquinidine may be proposed in children and in the patients who refuse the implant.

Introduction

Although the association between QT prolongation and sudden death has been known since the 1950s,[1–3] it has become necessary to wait until recent years to understand that short QT may also be related to an increased risk of sudden death. In fact, only recently the association between a familial history of sudden death[4] or atrial fibrillation (AF)[5] with a short QT interval has been recognized and short QT syndrome (SQTS) identified as a genetic disorder.[6–8]

Only one case of aborted sudden infant death has been reported to date,[4] but, in general little is known about the clinical presentation of SQTS, because the published data includes only a small number of patients.[4,5,7–10]

The aim of this study was to evaluate the clinical presentation, the occurrence of sudden infant death, the electrocardiographic (ECG) morphology, the prevalence of the known genetic mutations, and the results of the available

therapies at a mid-term follow-up in a relatively large group of patients with SQTS.

Methods

Inclusion criteria

This is an observational study designed to be partly prospective and partly retrospective. A total of 29 patients, 25 belonging to eight families and four sporadic cases (*Figure 1*), who had personal and/or a family history of sudden death or aborted sudden death and ECG documentation of short QT interval, were included in the study. Three out the these 29 patients were included after sudden death, having ECG documentation of short QT. The number of patients initially assessed was 14. After the screening of their family members, this number increased to 29. All patients gave their consent to the study protocol.

In the families, there were another 12 cases of sudden death without available ECG (*Figure 1*). For this reason, these subjects were not included in the study group. However, because all of them were apparently healthy people, who died suddenly, most <40 years of age, the association with SQTS may be hypothesized (*Figure 1*).

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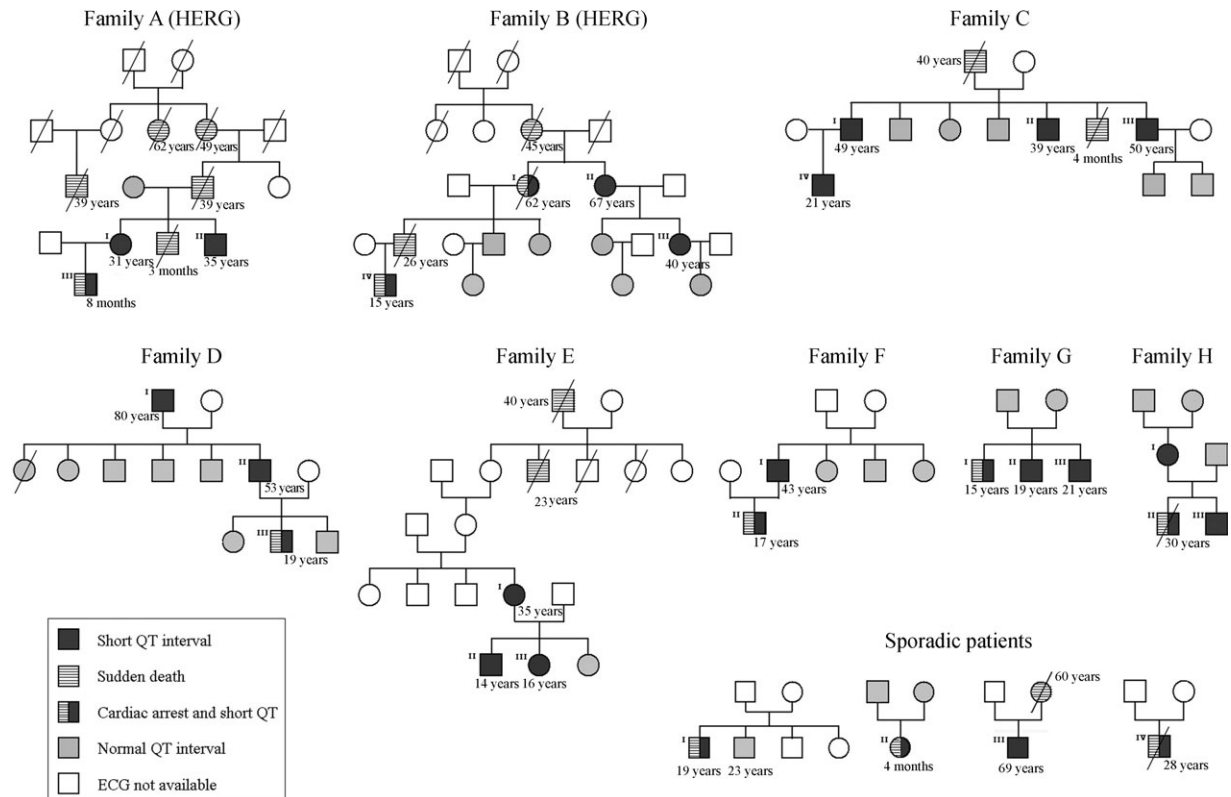
Figure 1 Family trees of the eight affected families and of the four sporadic patients. Circles indicate female; squares indicate male; symbols with a slash indicate deceased subjects. The age reported in subjects with sudden death or aborted sudden death indicates the age at the event, whereas in those with diagnosis of short QT and without cardiac arrest it indicates the age at the time of diagnosis.

A value of QT/QTp = 80% (where QTp is the predicted QT value following Rautaharju's formula),[11] as previously reported,[12] was chosen as the upper limit for short QT. These patients, all Caucasian, were referred to our institution from different countries. Familial and personal medical histories, paying particular attention to the cases of sudden infant death, were collected from each patient. The patients underwent an extensive evaluation, including physical examination, exercise stress testing, ECG, and cardiac magnetic resonance (MR), in order to rule out structural heart disease. Blood samples were taken to exclude any electrolyte abnormalities and to perform a genetic analysis.

QT measurement

The QT interval was evaluated in all 12-lead ECGs. The QT interval was measured at a speed of 25 or 50 mm/s and with a 200% magnification, usually in V_2, by two independent examiners. The QT was manually measured as the time interval between QRS onset and the point at which the isoelectric line intersected a tangential line drawn at the maximum downslope of the T-wave. The QT interval was corrected for the heart rate using Bazett's formula (QTc).[13]

The QT interval at different heart rates during the stress test was compared with the expected QT intervals using the Framingham linear regression formula,[14] as Bazett's formula may not be appropriate for correcting the QT interval for short cardiac cycle lengths.

Electrophysiological study

After informed written consent was obtained, a detailed electrophysiological study was carried out. Ventricular programmed stimulation was performed at two ventricular sites (right ventricular apex and outflow tract) at two or three different pacing cycle lengths, with two to three extrastimuli up to refractoriness, without any limits for the shortest coupling interval. Atrial programmed stimulation was performed at a pacing cycle length of 600 ms in the high lateral right atrium.

Therapeutic approach

The implant of an automatic implantable cardioverter-defibrillator (ICD) was proposed to all the patients, except the young children. In these latter patients, the decision to implant an ICD was considered after taking into account the weight and the age as well. The young children and the patients who refused the implant were treated with hydroquinidine, which had already been proved to prolong the QT interval in a previous study.[12]

Follow-up

The patients underwent regular outpatient visits at the reference centre.

Statistical analysis

Quantitative data was expressed as a mean ± SD or as a median, range, and interquartile range (IQR) as appropriate. Statistical analysis was performed using STATA® software (8.0). The probability of survival free from cardiac arrest, from birth and before the age of 40 years or before pharmacological therapy, was assessed using the Kaplan–Meier product-limit estimates. To assess the presence of predictors of the occurrence of cardiac arrest before therapy and accounting for possible within-group correlation, a shared frailty Cox proportional hazard regression model (latent familiar-level random effect) based on 12 clusters (eight families and one group for each sporadic patient) was fitted. The Cox model was used to estimate hazard ratios (HR) and corresponding 95% CI according to the potential prognostic variables sex and QTc.

All tests performed were two-sided and statistical significance level was set at 0.05.

Results

Clinical characteristics

Of the 29 patients, 21 were males and eight females. The median age at diagnosis was 30 years (IQR: 18–49 years; range 4–80). At the time of inclusion in the study, 18 out of 29 patients (62%) were symptomatic. Nine patients had a history of cardiac arrest (31%), resuscitated in six, two of whom had serious neurological damage. In eight of these nine patients cardiac arrest was the first clinical presentation. It occurred in patients from 4 months to 62 years of age. One more case of cardiac arrest was observed during the follow-up (patient IV, family B). The survival probability free from a first cardiac arrest is reported in *Figure 2*.

Six of the 29 patients had syncope and one patient presyncope (24%). In four (14%), this was the first clinical presentation. In three patients syncope was prolonged and resuscitation attempts were performed by bystanders; one episode occurred in an infant at 8 months of age (*Table 1*).

Nine patients (31%) had palpitations, with AF or flutter documented in seven (24%). In five patients (17%), AF was the first clinical manifestation. Two subjects had AF before 20 years of age, whereas in the other five AF occurred after 40 years of age. Frequent ventricular extrasystoles were documented in five patients.

Electrocardiography

The number of analysed ECGs for each patient was 1–8 with a median of 3 (IQR 2–5). In all the available ECGs, the QT/QTp interval was always <80%, with an absolute QT interval ≤320 ms, ranging from 210 to 320 ms, and a QTc ≤ 340 ms, varying from 250 to 338 ms. In most cases, the T-wave showed a narrow, peaked, high voltage, and symmetrical appearance and an ST-segment was almost absent (*Figure 3*). No relationship was observed between the T-wave amplitude and the prognosis, as cardiac arrest was observed both in subjects with high peaked T-waves and in the few subjects without high peaked T-waves.

The QTc interval was 300 ± 20 ms in the 10 patients with cardiac arrest and 309 ± 19 ms in the other 19 patients.

The sex and the QTc interval were evaluated in a multi-variable analysis to assess the presence of predictors of the occurrence of cardiac arrest. Neither the sex ($P = 0.275$), nor the QTc interval ($P = 0.319$) resulted to be significantly related to cardiac arrest. Syncope was not evaluated as a possible predictor of cardiac arrest, because the patients who presented syncope were subsequently treated.

Thirteen patients underwent an exercise stress test. A physiological heart rate increase was observed in all patients. Heart rate at rest was 71 ± 9 b.p.m., with a QT interval of 273 ± 19 ms. The maximum heart rate was 148 ± 32 b.p.m., with a mean QT interval of 233 ± 27 ms. With increasing heart rate, only a slight further reduction of the QT interval was observed and its values tended to be closer to the expected values.
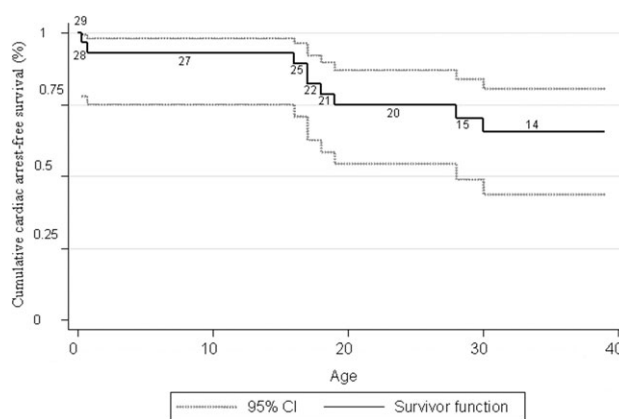
Figure 2 Kaplan–Meier estimate of cumulative survival free from cardiac arrest from birth to the age of 40 years or before pharmacological therapy in the 29 patients with SQTS. The CIs are reported.

Electrophysiological study

Eighteen patients underwent an electrophysiological study. The ventricular effective refractory period (ERP) at the right ventricular apex at a cycle length of 600–500 ms varied between 140 and 180 ms (mean 155 ± 12 ms) and at a pacing cycle of 430–400 ms varied between 130 and 180 ms (mean 150 ± 13 ms). Programmed ventricular stimulation was performed with two to three premature stimuli up to refractoriness, except in two patients in which extra-stimuli <180 ms were not used. Ventricular fibrillation was induced in 11 out of the 18 patients (61%): three had a history of aborted sudden death, four had syncope, two experienced palpitations, and two were asymptomatic. In seven patients, ventricular fibrillation was not induced: four were asymptomatic; two had a previous resuscitated cardiac arrest (in these two patients, two extrastimuli on two pacing cycle lengths up to 180 ms were used) and one patient was symptomatic for syncope, but later had a ventricular fibrillation interrupted by the ICD (this patient was studied using three extrastimuli on three pacing cycle lengths up to refractoriness).

As only three patients out of six with documented ventricular fibrillation were induced, the sensitivity of electrophysiological study was 50%.

Atrial ERPs were measured in the high lateral right atrium in 12 patients and at a cycle length of 600 ms varied between 120 and 180 ms, with a mean of 157 ± 22 ms.

Genetics and other diagnostic tests

Genetic screening was performed in all the eight families and in the sporadic patient I and III; HERG mutation (encoding for I_{Kr}) was found in two families (A and B, *Figure 1*), whereas none of the known mutations were found in six families and in the two sporadic patients. Concerning the other patients, the parents of the sporadic patient II have refused it and the sporadic patient IV died before genetic screening could be performed (*Table 1*).

The ECG was normal in all the patients. Eight patients underwent cardiac MR, which was normal in all of them.

Therapeutic approach

Of the 29 patients, three died before clinical evaluation, 14 received an ICD and 12 patients did not receive an implant

Table 1 Clinical characteristics of the 29 patients with SQTS

Patients	Sex	Age at observation (years)	Symptoms					Family history of SD	Mutation	ECG			
			Syncope	Cardiac arrest	Age at symptom	Circumstances of symptom	Comments			H.R. (b.p.m.)	QT (ms)	QTc (ms)	QT/QTp (%)
Family A													
I	F	31	Yes	–	30 years	At rest	Vaso-vagal	Yes	HERG	86	250	299	71
II	M	35	Yes	–	18 years	During effort	Running			66	270	283	68
III	M	6	–	Yes	8 months	Loud noise	Resuscitated			76	260	293	70
Family B													
I	F	62	–	Yes	62 years	Unknown	Sudden death	Yes	HERG	85	210	250	59
II	F	67	–	–	–	–	–			72	270	296	71
III	F	40	–	–	–	–	–			75	240	268	64
IV	M	15	Yes	a	8 months	During sleep	–			80	260	300	71
Family C													
I	M	49	–	–	–	–	–	Yes	Not found	73	275	303	73
II	M	39	Yes	–	29 years	During sleep	–			69	290	311	75
III	M	50	Yes	–	50 years	Daily activities	–			75	280	313	75
IV	M	21	–	–	–	–	–			64	300	310	75
Family D													
I	M	80	–	–	–	–	–	No	Not found	70	280	302	73
II	M	53	–	–	–	–	–			66	300	315	76
III	M	18	–	Yes	18 years	At rest	Resuscitated			78	270	308	73
Family E													
I	F	35	–	–	–	–	–	Yes	Not found	59	320	317	78
II	M	14	Yes	–	14 years	During effort	After intensive training			83	240	282	67
III	F	16	–	–	–	–	–			74	300	333	80
Family F													
I	M	43	–	–	–	–	–	No	Not found	82	290	338	80
II	M	17	–	Yes	17 years	Unknown	Resuscitated			115	210	291	69
Family G													
I	M	16	–	Yes	16 years	At rest	Resuscitated	No	Not found	77	280	317	76
II	M	19	–	–	–	–	–			73	294	324	78
III	M	21	–	–	–	–	–			65	320	333	80
Family H													
I	F	52	–	–	–	–	–	Yes	On going	67	310	327	79
II	M	30	–	Yes	30 years	During sleep	Sudden death			55	315	302	74
III	M	25	–	–	–	–	–			63	315	323	78
Sporadic patients													
I	M	21	–	Yes	19 years	During effort	Resuscitated	Yes	Not found	67	300	317	76
II	F	4	–	Yes	4 months	While awake	Resuscitated	Yes	Not done	128	210	307	73
III	M	69	Yes	–	62 years	Unknown	–	Yes	Not found	90	240	294	70
IV	M	28	–	Yes	28 years	Unknown	–	Unknown	Not done	65	300	312	75

aCardiac arrest during the follow-up, at the age of 17 years, during sleep, defibrillated by ICD.
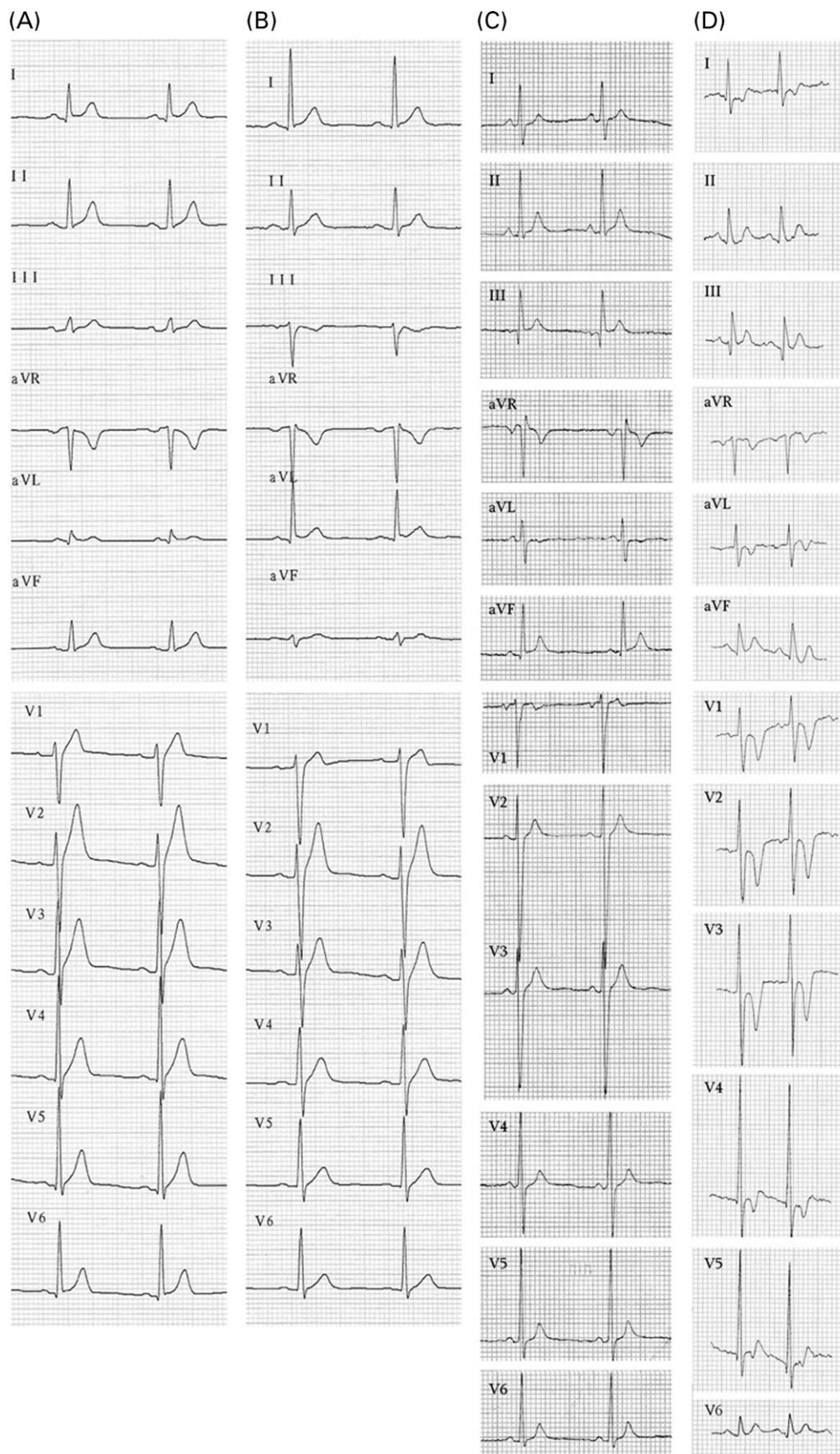
Figure 3 Twelve-lead ECG (25 mm/s paper speed) of four patients with SQTS. (*A*) Patient III, family C (50 years): sinus rhythm, heart rate 75 b.p.m., QT 280 ms, QTc 313 ms. (*B*) Patient II, family C (39 years): sinus rhythm, heart rate 69 b.p.m., QT 290 ms, QTc 311 ms. (*C*) Patient III, family A (6 years): sinus rhythm, heart rate 76 b.p.m., QT 260 ms, QTc 293 ms. (*D*) sporadic patient II (35 months): sinus rhythm, heart rate 143 b.p.m., QT 210 ms, QTc 324 ms. Note the deep negative T waves in leads V1–V3, which are the equivalent of the high peaked T-waves in adult patients.

as two patients were very young children and 10 patients refused the implant. The ICD was implanted in nine patients who had ventricular fibrillation induced at electrophysiological study. Of the other five patients, two had a previous resuscitated cardiac arrest, one had a history of syncope and two were asymptomatic. Seven patients who did not receive the ICD were started on hydroquinidine, as well as another three patients implanted with an ICD, who were symptomatic for episodes of AF. Of the 10 patients who received hydroquinidine, five had HERG mutation; these patients had an increase in the QTc from 289 ± 14 to 405 ± 26 ms, with a change score of 116 ± 18 ms. Moreover, in these patients an ST-segment became more evident and the T-waves increased in duration and decreased in amplitude (*Figure 4*). An electrophysiological study performed during therapy showed a mean ventricular ERP increase from 150 ± 12 ms to a mean of 200 ± 21 ms, with a change score of 66 ± 11 ms. In these patients ventricular fibrillation was not induced any more. In the other five patients without HERG mutation, the QTc increment was lower and less homogeneous, varying from 307 ± 22 ms to 352 ± 41 ms,

with a change score of 45 ± 25 ms. In this latter group, only the two patients with the higher QTc increase underwent an electrophysiological study during therapy: the ventricular ERP increased, respectively, from 160 to 200 ms and from 150 to 190 ms. Also in these patients ventricular fibrillation was not induced any more.

Children

Three children had aborted sudden death or syncope during infancy: patient III, family A; sporadic patient II and patient IV, family B.

Patient III, family A was observed at the age of 6 years. He had severe neurological damage as a consequence of aborted sudden death at the age of 8 months. An ECG recorded at the age of 35 months showed, at HR 120 b.p.m., a QT interval of 240 ms (QTc 339 ms, QT/QTp 80%). When he was 6 years old, he had, at HR 76 b.p.m., a QT interval of 260 ms (QTc 293 ms, QT/QTp 70%). He did not undergo an electrophysiological study because of the severe neurological damage; he was genotyped (HERG mutation).
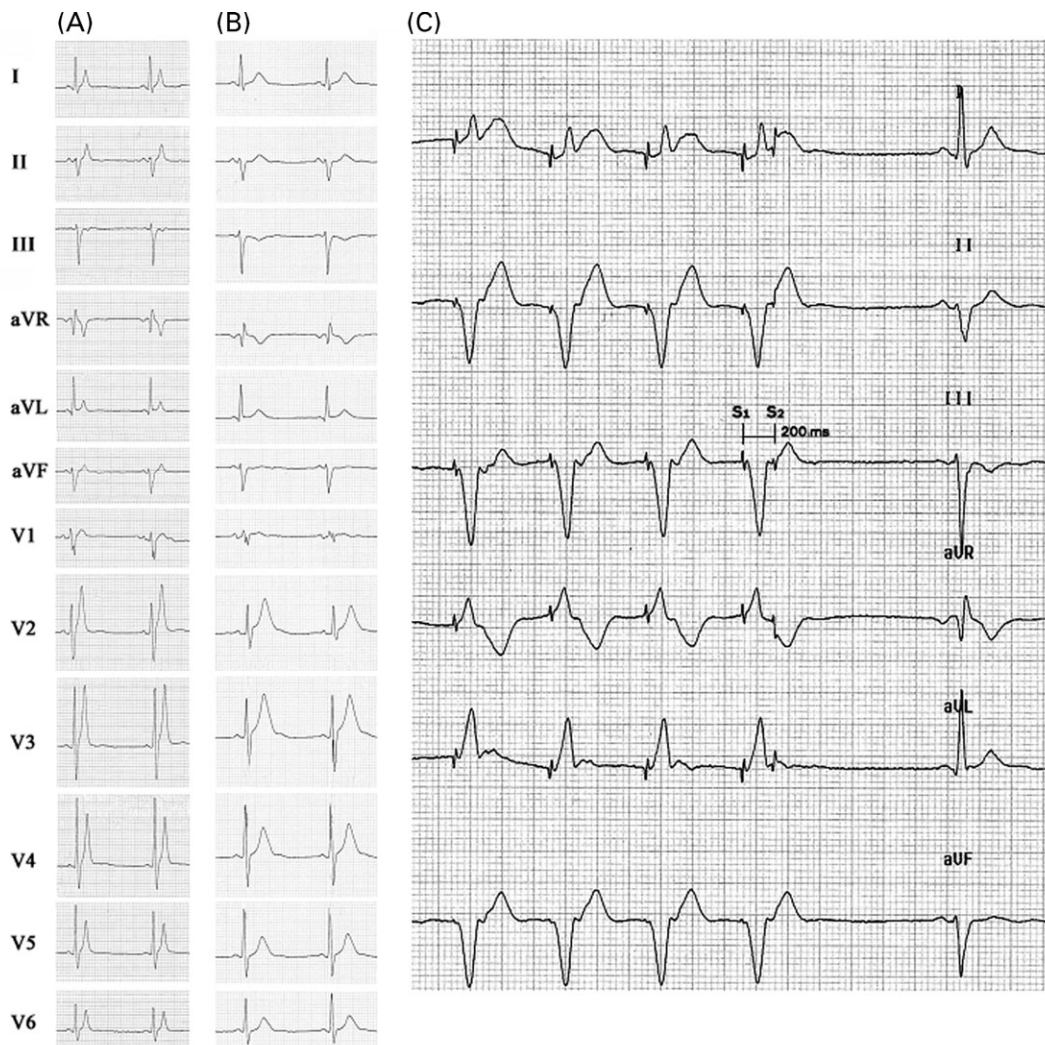
Figure 4 Twelve-lead ECG recordings of a short QT patient, showing hydroquinidine effect. From left to right: (*A*) basal ECG (sinus rhythm, heart rate 52 b.p.m., QT 280 ms, QTc 261 ms); (*B*) ECG during hydroquinidine administration (sinus rhythm, heart rate 60 b.p.m., QT 380 ms, QTc 380 ms). ST-segment appearance, T-wave duration increase, and T-wave amplitude reduction can be observed; (*C*) electrophysiologic study during hydroquinidine treatment shows a ventricular ERP of 200 ms.

The sporadic patient II was observed at the age of 4 years. She had an aborted sudden death at the age of 4 months. The child had two episodes of cardiac arrest treated with resuscitation manoeuvres; one of these occurred in the hospital and ventricular fibrillation was documented at ECG. When she was 8 months old an ECG showed, at HR 128 b.p.m., a QT interval of 210 ms (QTc 307 ms, QT/QTp 73%). An ECG recorded at the age of 35 months showed the following values: HR of 143 b.p.m., QT interval of 210 ms (QTc 324 ms, QT/QTp 78%). An electrophysiological study was tried when the child was 6 months old. The study had to be interrupted because ventricular fibrillation was induced twice by mechanical stimulation during catheter positioning. The genetic screening was not performed because of the parents' refusal.

The values of QT and QTc of these two children are below the minimum value for children of the same age reported in literature.[11,15]

Patient IV, family B experienced a syncope at the age of 8 months. SQTS was diagnosed at the age of 15 years; at this age, an ECG showed, at HR 80 b.p.m., a QT of 260 ms (QTc 300 ms, QT/QTp 71%). At the electrophysiological study there was no induction of ventricular arrhythmias. He received an ICD due to the short QT interval and the family history of sudden death over three generations. One year later he had an appropriate ICD discharge at night.[16] He has HERG mutation.

In the families studied there were two other babies which died suddenly: the infant which died at 3 months in family A and the one which died at 4 months in family C. These babies are shown in the family trees in *Figure 1*, but were not included in the study as they had no investigations performed during life, including ECG, as they were healthy.

Follow-up

For the 26 surviving patients included in the study, the median follow-up was 23 months (IQR: 20–35 months; range: 9–49). No patient died. Patient IV, family B, with a history of syncope and not inducible ventricular fibrillation, had an appropriate ICD intervention. In three patients, drug therapy was discontinued due to enteric side effects: two patients with an ICD did not receive any further antiarrhythmic therapy; the other one was a child (patient III, family A) with severe neurological sequelae due to a previous cardiac arrest and he was treated with flecainide and nadolol. The median follow-up of the seven patients in hydroquinidine was 29 months (IQR: 22–36 months; range 21–36).

None of the patients on hydroquinidine had documented or symptomatic AF episodes.

Discussion

Only in recent years an inherited short QT interval has been identified as a cause of familial sudden death.[4] As only a few families with different clinical histories are available, many questions remain unanswered. Little is known about what is the symptom prevalence associated with SQTS, what is the first clinical manifestation and at what age it can occur, what are the QT interval limits in the affected subjects, the role of the electrophysiological study in the stratification of the risk of sudden death, and the efficacy of the available therapies. This study analyses the clinical characteristics of 29 patients with SQTS, which up to now has been the largest group of patients reported.

Cardiac arrest was the most frequent symptom and the most frequent first clinical presentation. It was also observed in the first year of life, suggesting that this new ion channel disease may be one of the causes of the sudden infant death syndrome (SIDS). Syncope was observed less frequently and it occurred at any age. The most likely mechanism of syncope in SQTS, as in other channelopathies, is self-terminating VT/VF episodes.

Patients often presented palpitations, which were not only related to AF, but also to ventricular extrasystoles. AF was also observed in young patients and should presumably be related to the presence of short ERPs in the atria.

Concerning the ECG, in the first publication relating a short QT interval to familial sudden death, two families were described with QT and QTc ≤300 ms.[4] In this larger cohort of patients, the QT interval ranges from values as short as 210 ms to values of 320 ms; similarly the QTc varies from 250 to 340 ms. The multivariable analysis did not indicate the QTc interval as a significant risk factor for the occurrence of cardiac arrest, although it would be reasonable to suppose that a shorter QTc could predispose to a higher risk of ventricular arrhythmias. However, the absence of statistical significance might depend on the low number of patients.

A short QT interval is easier to recognize at low heart rates, whereas with increasing heart rates it tends to be closer to the normal values, as was observed, for example, during the exercise stress test. However, the QT values are still always below the normal values also at higher rates and this also makes possible the diagnosis in infants, who typically show high heart rates. This is particularly important considering that sudden death occurs also in the first months of life. It is likely that infants affected by SQTS could be identified by an ECG performed in the first months of life, as can be seen for those with long QT syndrome.[15] Besides the QT interval, also the T-wave morphology appears to be very important in order to identify short QT patients. High, peaked, and narrow T-waves particularly in the precordial leads appear to be the typical morphology of T-waves in congenital SQTS.

The electrophysiological study showed extremely short ERPs at both atrial and ventricular level. It is well known that short refractory periods cause a reduction in the wavelength (the product of refractory period and conduction velocity) and this might in itself explain atrial and ventricular vulnerability to arrhythmias. A heterogeneous shortening of the action potential duration among the different cell types spanning the ventricular wall has been proposed as an additional mechanism for re-entry responsible for tachycardia/fibrillation in SQTS.[17] Ventricular fibrillation was induced in most patients, however, the sensitivity of the electrophysiological study appears low and thus its value in defining the risk of sudden death in this population remains uncertain as the lack of ventricular fibrillation induction does not allow us to predict a good prognosis.

As far as genetics is concerned, mutations in three different genes have been linked to the SQTS until now: two different missense mutations in *KCNH2* (*HERG*), the gene

encoding for I_{Kr}, the rapidly activating delayed rectifier potassium channel, causing a gain of function in the channel,[6] two mutations in *KCNQ1* (*KvLQT1*), causing a gain of function in I_{Ks}, the slowly activating delayed rectifier potassium channel[7,18] and a mutation in *KCNJ2* (*Kir2.1*), causing a gain of function in I_{K1}.[8] However, the prevalence of these mutations does not seem high, as a mutation in HERG was found in only two of the families described in this study and neither a mutation in *KCNQ1* nor in *KCNJ2* was present in any of them. It is thus reasonable to suppose that mutations involving other genes will be identified in the future, similarly to what happened in long QT syndrome. The small number of genotyped families and the presence of a history of sudden death in all families does not allow us, up to now, to conclude that the genetic screening may help in identifying high-risk patients.

Because of the high incidence of sudden cardiac death, at the present time the implant of an ICD is the first choice therapy in patients with SQTS.[4] However, an ICD implant in very young children is technically difficult and is associated to a higher risk of complications through life compared with adults and, moreover, some patients refuse the implant. In these cases, hydroquinidine has been proposed, as it prolongs the QT interval and the ventricular ERPs and prevents ventricular arrhythmias induction in patients with HERG mutation.[12] However, in this study it was observed that patients without HERG mutation show a lower and less homogeneous QTc increment. In these patients, the effectiveness of hydroquinidine should be evaluated on the basis of individual cases. A quinidine test showing a marked QT interval prolongation could suggest a high probability of HERG mutation and could be useful in identifying potential responders to the drug.

Conclusions

SQTS is a genetic arrhythmogenic disorder with a high incidence of sudden death during life including the first months of life, and therefore should be considered as a possible cause of SIDS. The inheritance is autosomal dominant, with genetic heterogeneity. The diagnosis of short QT can be made with an ECG and it should always be considered in the presence of a family history of sudden death, particularly a history of sudden death in infants. It should also be considered in patients with idiopathic AF at a young age and in patients with syncope and a structurally normal heart. The outcome of SQTS patients becomes relatively safe when they are identified and treated. Unfortunately, without therapy the outcome is not so good. For this reason today, subjects with SQTS and family history of sudden death must be treated with ICD in primary prevention. At the moment there is no information on the prevalence of short QT in the general population. Further studies should also clarify whether subjects with short QT identified in a community-based survey have the same risk.

Conflict of interest: none declared.

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