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REVIEW

Short QT syndrome in pediatrics

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Abstract Short QT syndrome is a malignant cardiac disease characterized by the presence of ventricular tachyarrhythmias leading to syncope and sudden cardiac death. Currently, international guidelines establish diagnostic criteria when QTc is below 340 ms. This entity is one of the main diseases responsible for sudden cardiac death in the pediatric population. In recent years, clinical, genetic and molecular advances in pathophysiological mechanisms related to short QT syndrome have improved diagnosis, risk stratification, and preventive measures. Despite these advances, automatic implantable cardiac defibrillator remains the most effective measure. Currently, six genes have been associated with short QT syndrome, which account for nearly 60% of clinically diagnosed families. Here, we review the main clinical hallmarks of the disease, focusing on the pediatric population.

Keywords Sudden cardiac death · Short QT syndrome · Pediatrics · Genetics

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Introduction

The first study regarding alteration of the QT interval in the electrocardiogram (ECG) was published by Algra et al. [1]. In this study, a large cohort was followed up for 2 years. Risk implications of QTc interval variables were studied in patients without evidence of cardiac dysfunction or of an intraventricular conduction defect. The authors concluded that a prolonged and shortened mean QTc interval over 24 h was associated with a more than twofold risk of sudden cardiac death (SCD) compared with intermediate mean QTc values (400–440 ms). In 2000, a rare cardiac entity characterized by idiopathic persistent short QT interval in the ECG was described in three members of one family [2]. This new entity was called short QT syndrome (SQTS). Currently, almost 300 publications and nearly 80 families have been reported, most cases associated with a lethal outcome.

Large cohorts

In 2006, the first series of patients diagnosed with SQTS was published. This study included a total of 29 patients with SQTS and personal and/or familial history of cardiac arrest (median age at diagnosis was 30 years—range 4–80). Eighteen patients were symptomatic (62%): 10 had cardiac arrest (34%), and in 8 cases (28%), this was their first clinical presentation. Cardiac arrest had occurred in the first month of life in two patients. Seven patients had syncope (24%); 9 (31%) had palpitations with atrial fibrillation (AF) documented even in young subjects. Fourteen patients received an implantable cardioverter-defibrillator (ICD) and 10 hydroquinidine (HQ) prophylaxis. At a median follow-up of 23 months, only one patient received

an appropriate shock from the ICD; no patient on HQ had SCD or syncope. The study concluded that SQTS induces a high risk of SCD including in early infancy. The authors also recommended ICD as the first choice of therapy, but HQ could be proposed in children and in the patients who refuse the ICD [3]. In 2007, Antonnen et al. published the results of QT intervals of 10,822 randomly selected middle-aged Finnish subjects (5658 males, mean age 44+/−8,4 years) enrolled in a population study and followed-up for 29+/−10 years. The majority of subjects with short QT intervals were males. The authors concluded that a short QT interval does not appear to indicate an increased risk for all-cause or cardiovascular mortality in middle-aged non-referral, community-based individuals [4]. The first long-term follow-up of patients with SQTS was published in 2011 also by Giustetto et al. In this study, a total of 53 patients from the European Short QT Registry (75% males; median age 26 years) were followed for up to 64 ± 27 months. A familial or personal history of cardiac arrest was present in 89% of them and SCD was the clinical presentation in 32% (average QTc was 314 ± 23 ms), showing that SQTS induces a high risk of SCD in all age groups. Symptomatic patients have a high risk of recurrent arrhythmic events. Twenty-four patients received an ICD, and twelve patients received long-term prophylaxis with HQ, which was effective preventing the induction of ventricular arrhythmias. In 23% of index cases, the genetic analysis identified the cause of the disease [5].

Regarding pediatric population, the largest series of pediatric SQTS patients reported so far was published in 2013. In this study, a total of 25 patients were followed up for 5.9 years, the longest follow-up cohort of patients with SQTS reported in the literature. In this cohort, the age of patients was 21 years or younger (84% males), reflecting a sex-specific prevalence and possible greater vulnerability to SQTS in young males, as previously suggested by other authors. Median corrected QT interval for heart rate was 312 ms (range 194–355 ms), symptoms occurred in 56% and included aborted SCD in 6 patients (24%), and syncope in 4 patients (16%). The most common symptomatic presentation was cardiac arrest but also arrhythmias including AF, ventricular fibrillation (VF), supraventricular tachycardia (SVT), and polymorphic ventricular tachycardia (PVT). Genetic analysis identified the genetic cause associated with SQTS in 5 (24%) of 21 probands. Concerning family, 16 patients (84%) had a familial or personal history of cardiac arrest [6].

In 2014, the results of a database of 6.4 million ECGs obtained between 1995 and 2008 among 1.7 million persons were published. A QTc ≤ 300 ms was extraordinarily rare and was associated with significant ECG abnormalities and reduced survival [7]. The largest cohort of SQTS patients described so far was published in 2014 by Mazzanti et al. This study included 63 SQTS patients (84% male; age, 26 ± 15 years; corrected QT interval, 329 ± 22 ms), and 62 were followed for 60 ± 41 months (median 56 months). The authors showed that cardiac arrest (CA) was the most frequently presenting symptom (40% of probands; range < 1 month to 41 years). Arrhythmias occurred mainly at rest. The rate of CA was 4% in the first year of life and 1.3% per year between 20 and 40 years; in addition, the probability of a first occurrence of CA by 40 years of age was 41%. Despite the male predominance, female patients had also a risk profile superimposable to that of men ($p = 0.49$). Familial disease was present in 44% of kindreds, but the yield of genetic screening was low (14%). Finally, the authors concluded that CA is often the first manifestation of the disease with a peak incidence in the first year of life, recommending implantation of a defibrillator in SQTS infant patients [8].

Prevalence

European studies suggest a prevalence of 0.02–0.1% in the adult population, while, in pediatric population, the prevalence is 0.05% and male predominance [9]. Most events associated with SQTS usually happen in males. There is a suspicion that higher testosterone plasma levels may cause a shortening of the QT. In a recent study which measure ECGs in males with Klinefelter syndrome (KS) in comparison with controls, authors reported that QTc was shortest among testosterone (T)-treated males with KS, while untreated and thus hypogonadal KS had QTc interval comparable to controls. Genetic analysis did not identify mutations in any of genes associated with SQTS. These results suggest that genes on the X chromosome could be involved in regulation of the QTc interval and that T treatment may aggravate this arrhythmogenic mechanism [10]. Recently, in 2015, a study by *Sharma* et al. investigated the prevalence and significance of a short QT interval in a large population of healthy young individuals (age 14–35 years) in the UK. They concluded that the prevalence of a short QT interval depends on the recommended cut-off value and a definition of ≤320 ms is realistic to prevent overdiagnosis and excessive investigations [11].

Clinical assessment

Clinical manifestations may range from asymptomatic cases to irregular palpitations due to frequent paroxysmal AF, dizziness, ventricular arrhythmias, and syncope. Patients suffering from this entity usually have a family history of syncope or SCD in a young first or second degree family member. Hence, SQTS may cause sudden

cardiac death in infants (SIDS), children, and young adults. Accordingly to published data, when a patient is diagnosed, clinical assessment is recommended in all family members, including an ECG in newborns. Actually, current clinical data establish that there are two peaks of high risk of SCD associated with SQTS: in the first year of life and between age 20 and 40 [12]. For that reason, it has also been recommended to perform an ECG in the school screening program for disease detection. Despite low prevalence, some cases have been identified and usually remain asymptomatic but at high risk of SCD [13].

Diagnosis

The 2015 ESC guideline for diagnosis of SQTS is the presence of a QTc ≤340 ms (Class IC) in ECG or should be considered in the presence of a QTc ≤360 ms and one or more of the following: (1) a confirmed pathogenic mutation, (2) a family history of SQTS, (3) a family history of SD at age of 40 years, and (4) survival from a VT/VF episode in the absence of heart disease (Class IIaC) [14]. Other international guidelines/consensus documents define the SQTS as a genetic arrhythmogenic disorder characterized by a short and uniform QT/QTc intervals (<330 ms) on the ECG, with absent or minimal ST segments, with an interval from J point to T wave peak (Jp–Tp) measured in the precordial lead with the T wave of greatest amplitude <120 ms, possible tall T waves with narrow base similar to the T wave of moderate hyperkalemia ("desert tent T waves"), frequent early repolarization pattern, prolongation of T peak-T end interval, and possible presence of prominent U waves in the absence of structural heart disease and others disturbances that cause repolarization abnormalities (Fig. 1) [15–17]. Recently, Gollob et al. proposed a modified version of diagnostic criteria for SQTS, suggesting that may be useful in identifying patients at a higher risk for unexplained syncope, AF, or aborted SCD (Table 1), although larger cohort studies are necessary [6].

Diagnostic tools

When the diagnosis of SQTS is suspected, resting 12-lead ECG should be performed at a heart rate within normal limits [3, 18]. The QT interval should be measured when the heart rate is <100 bpm and preferably less than 80 bpm. The QT-RR relationship is generally less steep (lack of rate dependence) in patients with SQTS. As a consequence, QTc corrected by any formula will fail to reflect the true QTc. At rapid rates, QTc will falsely approximate normal values leading to a false-negative diagnosis. This is particularly important for the diagnosis in pediatric populations, where resting heart rate is 100 bpm [19, 20]. Furthermore, it has been suggested the PQ segment depression (PQD) as a novel marker for SQTS in addition to a short QT interval [17, 21]. Recent studies

Table 1 SQTS diagnostic criteria: 3 or more (indicating a moderate-to-high probability of SQTS)

SQTS diagnostic criteria	Points
QTc interval (ms)	
<370	1
<350	2
<330	3
J point-to-T peak interval <120 ms	1
Family history*	
First- or second-degree relative with high-probability SQTS	2
First- or second-degree relative with autopsy-negative	1
Sudden cardiac death	
Sudden infant death syndrome	1
Genotype*	
Genotype positive	2
Mutation of undetermined significance in a culprit gene	1

*Electrocardiogram must be recorded in the absence of modifiers known to shorten the QT interval. J point-to-T peak interval must be measured in the precordial lead with the greatest amplitude T wave. Family history points can be received only once in this section. *A minimum of 1 point must be obtained in the electrocardiographic section to obtain additional points

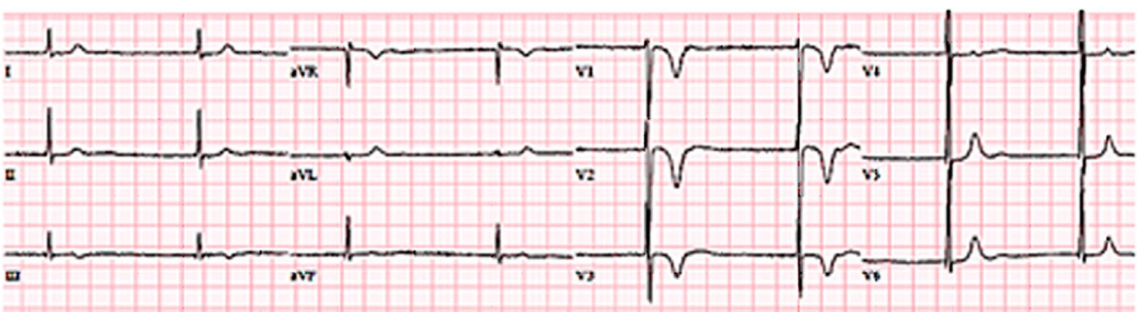

Fig. 1 Short QTc due to congenital short QT syndrome

suggest that exercise test can be also a useful tool in the diagnosis. Hence, patients with SQTS showed a reduced adaptation of the QT interval to heart rate [22]. In addition, it has been also recently reported that in SQTS, systolic function may also be affected and patients presented a significant dispersion of myocardial contraction. In consequence, tissue Doppler imaging (TDI) and speckle tracking echocardiography (STE) could become part of the assessment [23]. Invasive electrophysiological study with programmed ventricular stimulation is not recommended for SCD risk stratification [14].

Basic mechanisms

Watanabe et al. reported that patients with SQTS have a higher prevalence of early repolarization pattern in the ECG and that the presence of early repolarization is strongly associated with arrhythmic events [24]. Experimental studies suggest that the abbreviation of action potential in SQTS is heterogeneous with preferential abbreviation of either epicardium or endocardium, giving rise to an increase in transmural dispersion of repolarization (TDR). Dispersion of repolarization and refractoriness serve as substrate for re-entry in that it promotes unidirectional block. Marked abbreviation of wave length (product of refractory period and conduction velocity) is an additional factor promoting the maintenance of re-entry [24]. Recently, a new pathophysiological condition promoting SQTS has been published. Roussel et al. reported a SQTS in three patients from two unrelated families presenting a systemic carnitine deficiency. In all three patients, the ECG pattern was normalized with an oral carnitine therapy, suggesting a relationship between SQTS and carnitine deficiency [25]. This relationship was confirmed using a mouse model of carnitine deficiency induced by mildronate (3-(2,2,2-Trimethylhydrazinium) Propionate), a competitor inhibitor of OCTN2 [26, 27], suggesting that carnitine or its derivatives, especially long-chain acylcarnitines, should play a pivotal role in cardiac ionic currents, possibly leading to electrophysiological dysfunctions.

Animal models

Concerning animal models, rats, mice and especially kangaroos have been reported showing a short QT interval [28]. The major point of difference was the short duration of the red kangaroo ventricular action potential compared to those of the placental mammals, and compared to atrial cells from the kangaroos. This explains the short QT interval reported by others for kangaroo ECG, and that it may also be implicated in the high frequency of SCD previously noted in these animals [28]. In 2010, a canine model of SQTS was published showing that information gained from canine studies mimic observations in man qualitatively [29]. Recently, several zebrafish lines have emerged as novel vertebrate models for human arrhythmia disorders such as SQTS. Because of its size and the high number of progeny, zebrafish are very suitable for rapid *in vivo* analysis of the bioactivity of small molecules and their therapeutic potential [30].

Genetic basis

The first genetic alteration associated with SQTS was identified in the *KCNH2* gene [31]. Ten years after, nearly 30 pathogenic alterations in six genes have been published following an autosomal dominant pattern of inheritance and high penetrance [32]. Currently, there are three genes encoding potassium channels (*KCNQ1, KCNJ2, and KCNH2)*, and three more genes encoding calcium channels (*CACNA1C, CACNB2*, and *CACNA2D1*). Therefore, a comprehensive genetic analysis identifies the cause of the disease in nearly 60% of clinically diagnosed cases, remaining 40% of families without a genetic cause identified [33]. This limitation difficult comprehensive genotype–phenotype studies, a crucial step in clarifying the origin, pathophysiology, and outcome of the disease. Recent studies suggest that clinical characteristics of SQTS can differ depending on the patient genotype, as is observed in LQTS [34]. It may help clinicians to stratify the risk of ventricular arrhythmias and SCD in families suffering of SQTS (Table 2; Fig. 2).

Potassium genes (*KCNQ1, KCNJ2*, and *KCNH2*) encode membrane channels proteins playing a key role in potassium currents, inducing a gain of function, and, therefore, shortened repolarization. Concretely, the *KCNH2* gene (ID: 3757) encodes a voltage-activated potassium channel belonging to the ether-a-go-go (EAG) family-potassium voltage-gated channel, subfamily H (EAG-related), member 2. Its function is pore-forming (alpha) subunit of voltage-gated inwardly rectifying potassium channel. Channel properties are modulated by cAMP and subunit assembly. It mediates the rapidly activating component of the delayed rectifying potassium current in heart (IKr). The *KCNH2* gene is localized at chromosome 7 (7q36.1)—150,642,044 to 150,675,403—with a size of 33,360 bases (1159 amino acids; 126655Da). In general, cardiac events are associated with adrenergic in situations such as noise or exercise, but also occurred at rest [34]. The second gene associated with SQTS is *KCNQ1* (ID: 3784). The *KCNQ1* gene is localized at chromosome 11 (11p15.5)—2,465,914 to 2,870,340—with a size of 404,427 bases (676 amino acids; 74699Da). This gene encodes a voltage-gated potassium channel

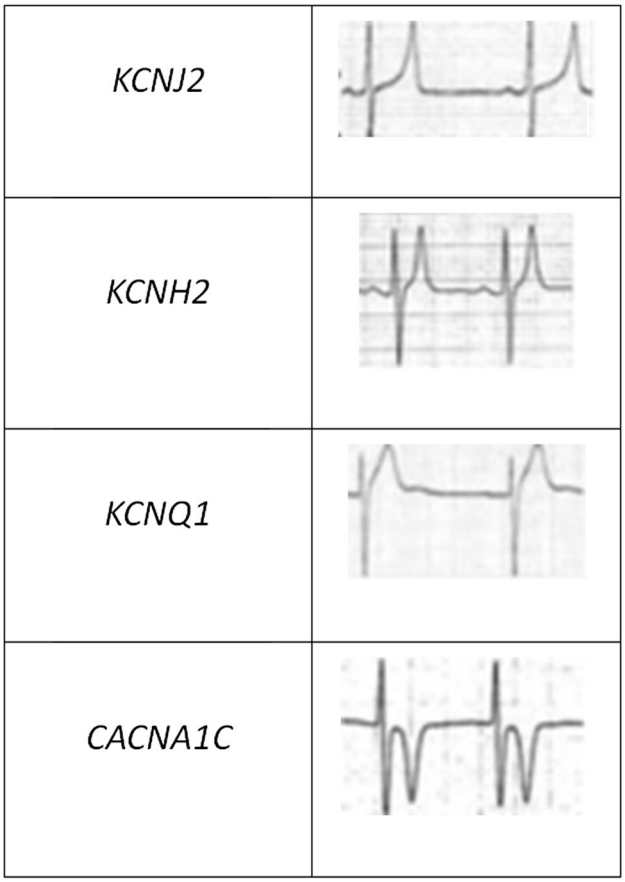

Fig. 2 Electrocardiogram associated with genotype

required for repolarization phase of the cardiac action potential. This protein can form complexes associated with two other potassium channel proteins, KCNE1 (gene *MinK*) and KCNE3 (gene *MiRP2*). When it is associated with KCNE1, it forms the I(Ks) cardiac potassium current and induces a rapid activation of potassium-selective outward current [35]. The *KCNQ1* gene may be also associated with KCNE3 protein to form the potassium channel [36]. In 2013, Maltret et al. reported a baby girl showing fetal bradycardia, slow sinus rhythm with an extremely short QT interval duration but also with vestibular dysfunction. Genetic analysis identified the same variant [37]. One year after, this interesting entity was also published in two new unrelated patients [38]. Recently, a group published a follow-up of 20 years, reporting a progressive evolution from sinus node dysfunction to low-rate atrial fibrillation [39], in concordance to our recent publication focus on follow-up of 3 patients suffering of this entity. All three carry the same *de novo* pathogenic mutation, p.V141M_*KCNQ1*. We recommend genetic analysis in patients with similar clinical findings. The last potassium gene is *KCNJ2* (ID: 37591). The protein encoded by this gene is an integral membrane protein and inward-rectifier-type potassium channel. Inward-rectifier potassium channels are characterized by a greater tendency to allow potassium to flow into the cell rather than out of it. Their voltage dependence is regulated by the concentration of extracellular potassium; as external potassium is raised, the voltage range of the channel opening shifts to more positive voltages. This gene is localized at chromosome 17 (17q24.3)—68,164,814 to 68,176,189—with a size of 11,376 bases (427 amino acids; 48288Da) [40–42]. Recently, it was reported a new pathogenic variant (p.K346T, c.1037A>C) inducing a gain-of-function mechanisms relevant to understand SQTS pathogenesis, suggesting the potential association of SQTS with neurological disorders [43].

Regarding calcium channels, the most important is *CACNA1C* (ID: 775). This gene encodes an alpha-1 subunit of a voltage-dependent calcium channel (calcium channel, voltage-dependent, L type, alpha 1 C subunit). Voltage-sensitive calcium channels (VSCC) mediate the entry of calcium ions into excitable cells and are also involved in a variety of calcium-dependent processes. It is localized at chromosome 12 (12p13.33)—2,079,952 to 2,807,115—with a size of 727,164 bases (2221 amino acids; 248977Da). All variants identified have been associated with an entity which combines BrS and shorted-than-normal QT interval. The combination of BrS pattern with a shorter QT interval has been associated with pathogenic variants in two genes:*CACNA1C* and *CACNB2*. Other calcium gene is *CACNB2* (ID: 783). This gene encodes a subunit of a voltage-dependent calcium channel protein that is a member of

Table 2 Genes associated with short QT syndrome (SQT)

Channel	Disease	Inheritance	Locus	Gene (ID)	Protein
Potassium	SQT 1	AD	7q35	*KCNH2* (3757)	hERG Kv11.1
	SQT 2	AD	11p15.5	*KCNQ1* (3784)	Kv7.1
	SQT 3	AD	17q23	*KCNJ2* (3759)	Kv2.1 Kir2.1
Calcium	BrS and shorter QT (SQT 4)	AD	2p13.3	*CACNA1C* (775)	Cav 1.2
	BrS and shorter QT (SQT 5)	AD	10p12.33	*CACNB2b* (785)	Voltage-dependent b-2
	SQT 6	AD	7q21-q22	*CACNA2D1* (781)	Voltage-dependent a2/d1

BrS Brugada syndrome, *AD* autosomic dominant

the voltage-gated calcium channel superfamily. The beta subunit of voltage-dependent calcium channels contributes to the function of the calcium channel by increasing peak calcium current, shifting the voltage dependencies of activation and inactivation, modulating G protein inhibition, and controlling the alpha-1 subunit membrane targeting. It is localized at chromosome 10 (10p12.33)—18,429,606 to 18,830,798—(401,193 bases, 660 amino acids; 73581Da) [44]. As mentioned before, this variant was reported giving the association BrS and shortened QT interval. The third calcium gene is *CACNA2D1* (ID: 781). This gene encodes a member of the alpha-2/delta subunit family, a protein in the voltage-dependent calcium channel complex. The alpha-2/delta subunit of voltage-dependent calcium channels regulates calcium current density and activation/inactivation kinetics of the calcium channel. It is localized at chromosome 7 (7q21-q22)—81,575,760 to 82,073,114—(497,355 bases, 1103 amino acids; 124568Da) [45]. Only one variant has been reported so far, but it has also been identified in control population despite Minor Allele Frequency (MAF) minor 1% [46].

Molecular autopsy

Several studies focused on genetic analysis in post-mortem samples have been published. The cohort of samples always refers to sudden death victims, most part of times under 30 years old, without a conclusive cause of death after complete autopsy. Due to normal heart, arrhythmic cause of death is highly suspected. Hence, recent forensic guidelines recommend performing molecular autopsy in these cases. The most plausible cause of death is a channelopathy, such as SQTS. Genetic analysis of genes associated with SQTS may identify the genetic alteration as potential cause of death. In addition, due to inherited disease, genetic analysis of relatives may help to identify genetic carriers at risk, sometimes even asymptomatic [47]. Cardiac ion channel genetic testing in autopsy-negative sudden death victims has a high diagnostic yield, with identification of the disease in 40% of families. They concluded that first-degree family members should be offered predictive testing, clinical evaluation, and treatment with the ultimate goal to prevent SCD [48].

Treatment

The most favorable strategy for primary prevention in SQTS is still discussed given the lack of independent risk factors, including syncope, for cardiac arrest. An ICD is the first and more effective therapeutic measure in patients who have experienced sustained VT/VF episodes or survivors of an aborted cardiac arrest [49]. Although intuitively, it might seem reasonable to suggest that patients with the shortest QTc values are at highest risk, clinical data do not support this hypothesis and the implantation of an ICD in asymptomatic patients with SQTS [50]. Recently, it has been suggested that an ICD might be implanted in patients with a strong family history of SCD and the previous evidence of short QTc. An alternative to ICD is the pharmacological approach, with administration of Quinidine which induces a QT-prolongation (Class IIbC). Early approaches to medical therapy in SQTS included use of QT-prolonging drugs. Sotalol, a prototypical QT-prolonging drug, is ineffective in patients with *KCNH2* mutations (SQTS1), the most common subtype. It was subsequently recognized that most QT-prolonging drugs have the highest affinity to the inactivated state of I_{Kr}. Given that SQTS1 typically is the result of a mutation in *KCNH2*, which impairs inactivation of I_{Kr}, the relative resistance to these medications is understood. Quinidine, which has similar affinity to the open and inactivated states of I_{Kr}, is effective therapy for SQT1. The effectiveness of Quinidine has been supported by the recent long-term follow-up from the European Short QT registry. A common complication in patients who received an ICD was the inappropriate shocks and an appropriate programming of the ICD is needed to prevent inappropriate ICD shocks from T wave oversensing due to tall T waves.

Conclusion

Pediatric population diagnosed with SQTS is at high risk of SCD. An ECG in newborns should be performed in families suffering of SQTS. Despite recent advances risk stratification remains a major current challenge for clinicians. Implantation of an ICD is the most effective therapy despite pharmacological treatment should be considered. Notwithstanding the advances in genetics, nearly 40% of families remain without a genetic cause identified. Clinical and genetic analysis is crucial to improve current guidelines and prevention of SCD in families suffering of SQTS.

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Compliance with ethical standards

Conflict of interest None.

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