FAMILIAR, CONGENITAL OR HEREDITARY SHORT QT SYNDROME: "GUSSAK SYNDROME". UPDATE

Abstract

Hereditary, familiar or congenital short QT syndrome (SQTS) is a rare clinical-electrocardiographic, sporadic or hereditary familial autosomal dominant entity without (hasta la actualidad) demonstrable structural heart disease ("electrical disease") considered the newest channelopathy.

The syndrome may affect fetus, newborn, infants, children, adolescents or young adults and is characterized on ECG by a very short OT interval (QTc equal or minor than 320 ms), a short or even absent ST segment and frequent tall T waves with narrow bases and pseudo symmetrical shape associated with high risk of paroxysmal atrial fibrillation (AF), syncope or sudden cardiac death (SCD) due to rapid malignant ventricular tachycardia (VT). In all of cases the electrophysiological substrate is a heterogeneous abbreviation of atrial and ventricular refractory period and action potential duration (APd).

Programmed Electrical Stimulation (PES), causes frequently induction of these arrhythmias.

The safest treatment indicated is implantable cardioverter-defibrillator (ICD).

The ability of quinidine to prolong the QT interval has the potential to be an effective therapy.

Key words: Congenital Short QT Syndrome – Sudden Cardiac Death – Channelopathy – Electrical disease.

Introduction: Familiar, hereditary, or congenital or SQTS is a newly described channelopathy entity without demonstrable structural heart disease (hasta la

actualidad y con los métodos diagnósticos disponibles) ("electrical disease") sporadic or familial with autosomal dominant transmission characterized on ECG by a very short OT interval (corrected QT interval (QTc) equal or minor than 320 ms), a short or even absent ST segment and tall pseudo symmetrical T waves with narrow bases and high risk of paroxysmal AF, syncope or SCD due to malignant VT (sometimes a short-coupled variant of Torsade de Pointes. **Lu LX, Zhou W, Zhang X, Short QT syndrome: a case report and review of literature. Resuscitation. 2006; 71:115-121.**)

The possible electrophysiological substrate for the development of paroxysmal AF and VT may be a significant transmural dispersion of the repolarization due to a heterogeneous abbreviation of the action potential duration (APd) and refractory period in both atrial and ventricular wall. **Schimpf R, Wolpert C, Gaita F, Short QT syndrome. Cardiovasc Res. 2005; 67: 357-366**.

In ventricles, transmural voltage gradients developing as a result of difference in the time course of repolarization of the epicardial, M, and endocardium cell APs, and the more positive plateau potential of the M cell contribute to inscription of the ST segment, T and U waves. Amplification of these heterogeneities can results in abnormalities of the ST segment (J wave), T wave, U wave and QT interval leading to the development of the Brugada, long QT, and short QT syndromes. **Antzelevitch C. Cellular basis for the repolarization waves of the ECG. Ann N Y Acad Sci. 2006; 1080: 268-281.**

Historical aspects: Chronology of the discovery

Year 1993: The first data suggesting that not only too long but also too short a QT interval (lesser than 400 ms) may be associated with increased risk of sudden cardiac death (SCD). Algra et al **Algra A, Tijssen JGP, Roelandt JRTC, et al. QT interval variables from 24-Hour electrocardiography and the 2- Year risk of sudden death. Br Heart J. 1993; 70:43-48.** studding a Cohort of 6693 consecutive patients who underwent 24-hour electrocardiography followed up for 2 years. Of these, the authors observed that prolonged and a shortened mean QTc interval over 24 hours was associated with a more than two fold risk of SCD compared with intermediate

mean QTc values (400 to 440 ms). Neither short nor long term variability in QTc had a distinct relation with the risk of SCD.

Year 2000: Gussak et al, (**Gussak I, Brugada P, Brugada J, et al. Idiopathic short QT interval: a new clinical syndrome? Cardiology. 2000; 94: 99-102.** related the first clinical report of an idiopathic familial persistently short QT interval, in three members of one family. A 17 girl teenager component of the family showed repetitive episodes of paroxysmal AF. Similar ECG changes seen in an unrelated 37-year-old patient were associated with SCD. The authors considered the possible arrhythmogenic potential of the short QT interval and the possibility of a new familiar clinical syndrome. We propose the just eponym "Gussak syndrome".

Year 2004: Brugada et al. working in the Masonic Medical Research Laboratory identified the first genetic defect of this new clinical entity. Later, with the discovery of others mutations this variant will be named SQT1. The mutation causes a gain of function in rapid delayed rectifier current (IKr). The study was the result of a collaborative effort among researchers in Europe, and the United States (**Brugada R, Hong K, Dumaine R, et al. Sudden death associated with short-QT syndrome linked to mutations in HERG. Circulation. 2004; 109: 30-35**.).

Year 2004: Bellock et al **Bellocq C, van Ginneken AC, Bezzina CR, et al. Mutation in the KCNQ1 gene leading to the short QT-interval syndrome. Circulation. 2004; 109:2394-2397** identified the second genetic defect in this new clinical entity. This is the SQT2 variant with mutation in slow delayed rectifier current (IKs)

Year 2005: Priori et al **Priori SG, Pandit SV, Rivolta I, et al. A novel form of short QT syndrome (SQT3) is caused by a mutation in the KCNJ2 gene. Circ Res. 2005; 96:800-807** identified the third genetic defect in this new clinical-electrocardiographic entity. The variant, named SQT3 has the mutation in the KCNJ2 gene that affect the inward rectifier K^+ current IK_1. This channel is responsible for the maintaining resting membrane potential in atria, His-Purkinje, and ventricular cells.

Year 2007: Antzelevitch et al. **Antzelevitch C, Pollevick GD Cordeiro JM, et al. Loss-of-function mutations in the cardiac calcium channel underlie a new clinical entity characterized by ST-segment elevation, short QT intervals, and sudden cardiac death. Circulation. 2007; 115: 442-449.** Identified mutations in the L-type calcium channel associated with a familial SCD syndrome in which a mixed phenotype was observed: Brugada syndrome combined with discreet short QTc interval.

Age of presentation:

The entity affects mainly young adults, adolescent and infants. Thirty years old is the median age at diagnosis (range 4-80).**Giustetto C, Di Monte F, Wolpert C, et al. Short QT syndrome: clinical findings and diagnostic-therapeutic implications. Eur Heart J. 2006; 27: 2440-2407.).** SQTS may be a cause of death in utero, newborns and early infancy.

Genetic background

At present, three sub types were described:

1) **SQT1:** Caused by 2 different missense mutations resulting in the same amino acid change (N588K) in the S5-P loop region of the cardiac IKr channel HERG (HERG: Human Ether-a-go-go-Related Gene) (KCNH2). **Brugada R, Hong K, Dumaine R, et al. Sudden death associated with short-QT syndrome linked to mutations in HERG. Circulation. 2004; 109: 30-35.** Gene led to an increase in the function of Ikr (SQT2). Mutations on Human Ether-a-go-go-Related Gene are responsible for congenital LQTS, SQTS, muscular atrophy and many forms of cancer. **Witchel HJ. The hERG potassium channel as a therapeutic target.Expert Opin Ther Targets. 2007; 11: 321-336.**
2) **SQT2:** Caused by mutation in the KCNQ1 gene.A g919c substitution in KCNQ1 encoding the K+ channel KvLQT1. (**Bellocq C, van Ginneken AC, Bezzina CR, et.al. Mutation in the KCNQ1 gene leading to the short QT-interval syndrome. Circulation. 2004;109(20):2394-2397.**). Mutations V307L in KCNQ1 voltage-activated potassium channel alpha-subunit(IKs) are responsible for at least five channelopathies the

Romano-Ward syndrome, the Jervell and Lange-Nielsen syndrome (cardioauditory syndrome), **Jervell and Lange-NielsenCongenital deaf-mutism, functional heart disease with prolongation of the Q-T interval and sudden death.Am Heart J. 1957;54:59-68**)) the SQT1, genetic AF, AF and SQTS in association. There is a description of a novo missense KCNQ1 mutation (V141M) responsible for AF and SQTS in uterus. **Hong K, Piper DR, Diaz-Valdecantos A, et al. De novo KCNQ1 mutation responsible for atrial fibrillation and short QT syndrome in utero. Cardiovasc Res. 2005;68:433-440.**

3) **SQT3:** Caused by mutation in the KCNQ1 geneMutation in the KCNJ2 gene, lead to an increase in the function of Ik1 channel.(SQT3) the KCNJ2 gene encoding the strong inwardly rectifying channel protein Kir2.1. The affected members of a single family had a G514A substitution in the KCNJ2 gene that resulted in a change from aspartic acid to asparagine at position 172 (D172N). **Priori SG, Pandit SV, Rivolta I, et al. A novel form of short QT syndrome (SQT3) is caused by a mutation in the KCNJ2 gene. Circ Res. 2005;96:800-807.)**

Gain-of-function ion channel mutations in cardiac potassium channel genes are the currently known cause of SQTS and obvious genetic heterogeneity is evident from the few reported families. **Schulze-Bahr E. Short QT Syndromes Herz. 2006;31:118-122**;

All encoding cardiac ionic potassium channels have been identified in affected patients. Mutations of Ikr, Iks, Ik1 channels cause dysfunctional Iks, Ikr, Ikl channels with an increase in the net outward K current leading to shortening of atrial and ventricular repolarization.

Recently Antzelevitch et al. **Antzelevitch C, Pollevick GD Cordeiro JM, et al. Loss-of-function mutations in the cardiac calcium channel underlie a new clinical entity characterized by ST-segment elevation, short QT intervals, and sudden cardiac death. Circulation. 2007; 115:442-449.** identified mutations loss-of-function missense mutations in CACNA1C (A39V and G490R) and CACNB2 (S481L) encoding the alpha1- and beta2b-subunits of the L-type calcium channel associated with a familial SCD syndrome in which a Brugada

syndrome phenotype was combined with corrected QT intervals shorter-than 360 ms, and QTc ranged from 330 to 370 ms among probands Confocal microscopy revealed a defect in trafficking of A39V Ca(v)1.2 channels but normal trafficking of channels containing G490R Ca(v)1.2 or S481L Ca(v beta2b)-subunits.

We observed that ECGs pattern of Antzelevitch manuscript have absent or extremely short ST segment with Q-aT = 240ms.

The QT interval can be divided into QoT, QaT, and QeT intervals, which are measured from the beginning of the QRS complex to the origin (o), apex (a), and the end (e) of the T wave, respectively. (Figure 1).

Q-aTc: From the beginning of QRS complex to apex of T wave corrected for heart rate. Q-aTc interval is the more easily and precisely measured at elevated calcium levels and exhibited the strongest correlation over the range of calcium levels measured. The relation is linear and could be used to estimate serum calcium levels from measured Q-aTc intervals. **Nierenberg DW, Ransil BJ. Q-aTc interval as a clinical indicator of hypercalcemia. Am J Cardiol 44: 243–248, 1979**.),

When all other factors known to affect the Q-T interval are ruled out, the shortening of the Q-aTc interval (≤270ms) appears to be a useful clinical indicator of hypercalcemia. We think that this new mutation has an ECG phenotype hypercalcemic like.

Atrial fibrillation tendency:

The syndrome is frequently associated with paroxysmal AF. Atrial and ventricular refractory periods are short, because a gain of function and a shortening of the AP duration both in atria and ventricle with consequent AF and VF tendency. There is high incidence of paroxysmal AF in proband and eventually in family members.

Clinical spectrum

Interrogatory data

The clinical spectrum of SQTS is very wide ranging from asymptomatic (≈38%) carriers to syncope or SCD. **Lupoqlazoff JM, Denjoy I. Familial short QT syndromeRev Prat. 2007;57:121-125.**

The channelopathy together with LQST show a high degree of genetic heterogeneity of the molecular pathways in terms of the relationships between genetic defects and phenotypic expression. **Borchert B, Lawrenz T, Stellbrink C.Long and short QT syndrome. Herzschrittmacherther Elektrophysiol. 2006;17: 205-210.)**

Symptomatic: (≈62%)

1) Positive family history of SCD in relatives of first degree;
2) Resuscitated SCD;
3) Positive history of paroxysmal AF;
4) Documented VF;
5) Cardiac arrest (34%) and in 8 (28%) this was the first clinical presentation. Cardiac arrest is possible in the first months of life.. SQTS may also account for deaths classified as sudden infant death syndrome. **Morphet JA.The short QT syndrome and sudden infant death syndrome.Can J Cardiol. 2007; 23:105.**
6) Personal history of palpitations is observed in ≈31% of cases;
7) Dizziness ranging from lightheadedness, unsteadiness to vertigo;
8) Syncope (24%);
9) Cardiac arrest.

Physical findings When an episode of paroxysmal A

The clinical spectrum is very wide ranging from asymptomatic carriers to syncope or SCD.

Electrocardiogram (ECG) It is important to recognize this ECG pattern because it is related to a high risk of SCD and paroxysmal AF in young, otherwise healthy subjects.

Short QT/QTc interval: Patients with SQTS are characterized by rate-corrected QT intervals (QTs) less than 320 ms.≤ 40 ms. Shortened QT interval of less than 300-325 ms after correction for heart rate at rates below 80 beats per minute. Short QTc reported by an ECG computer is inaccurate and required manual correction. SQTS, defined as QTc equal or minor than 300 ms, is very rare. Reining et al were unable to find one patient among a population 106,432 patients with a true QTc <300 ms.**Reinig MG, Engel TR.The Shortage of Short QTs. Chest. 2007 Apr 5; [Epub ahead of print].** From a reviewed of 12,012 ECGs) who underwent routine medical examinations for occupational reasons, the shortest QTc encountered was 335 ms. A QTc interval equal or minor than 330 ms is extremely rare in healthy subjects, and the presence of a QT interval in the lowest 1/2 centile of the normal range does not imply a significant risk of SCD. **Gallagher MM, Magliano G, Yap YG, Distribution and prognostic significance of QT intervals in the lowest half centile in 12,012 apparently healthy persons. Am J Cardiol. 2006;98:933-935.).**

T waves: Tall and narrow T waves. Probably, specific T-wave patterns make each subtypes recognizable. SQT3 variant has asymmetrically shaped T waves. **Priori SG, Pandit SV, Rivolta I, et al. A novel form of short QT syndrome (SQT3) is caused by a mutation in the KCNJ2 gene. Circ Res. 2005;96:800-807**

Atrial fibrillation: Repetitive episodes of paroxysmal AF are frequent. **Gussak I, Brugada P, Brugada J, et al. Idiopathic short QT interval: a new clinical syndrome? Cardiology. 2000; 94:99-102).**

Rapid polymorphic VT/VF.

Exercise stress testing: Lack of adaptation of QT interval duration is observed during increasing heart rates. **Borggrefe M, Wolpert C, Antzelevitch C, et al. Short QT syndrome. Genotype-phenotype correlations. J Electrocardiol. 2005; 38:75-80**.

Electrophysiological study: During programmed electrical stimulation, atrial and ventricular effective refractory periods are very shortened (≈130 milliseconds), and in a high percentage, AF or VT/VF are inducible with three short coupled extrastimuli.

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Morphological evaluation Autopsy did not reveal any structural heart disease .

Management

As of today, ICD is the only effective treatment for the prevention of SCD in the hereditary short QT syndrome. ICD therapy may be associated with an increased risk of inappropriate therapies for T wave oversensing, which, however, can be resolved by reprogramming ICD detection algorithms.

Patients without a family history of SCD or symptoms need a defibrillator cannot yet be answered, and requires further investigation. The possibility of the recurrence of numerous shocks while the patient is conscious must always be explained to the patients. These shocks are sometimes inappropriate, and may lead to psychological problems and suicide in teenagers **Schwartz PJ: The long QT syndrome .In: Camm AJ (ed): Clinical Approaches. Tachyarhythmias Series, Armonk, NY, Futura Publishing, 1997.**

Pharmacological approach: for AF prophylaxis and for reducing the number of ventricular arrhythmic events (and ICD discharges). Additionally in may be proposed as and adjunct to ICD therapy or as possible alternative treatment especially for children , newborns and in the patients who refuse the implant.

Drugs armamentarium

1) **Hydroquinidine** prophylaxis: effectively suppressed gain-of-function in IKr, along with prolongation of the QT interval. In patients with a mutation in HERG (SQT1), quinidine rendered VTs noninducible and restored the QT interval/heart rate relationship toward a reference range. In this specific patient population, quinidine proved to be efficient in prolonging the QT interval and normalizing the effective refractory periods.**Wolpert**

C, Schimpf R, Veltmann C, Clinical characteristics and treatment of short QT syndrome. Expert Rev Cardiovasc Ther. 2005; 3:611-617.) This is particularly important in developing countries, where the ICD therapy is not always available. Since these patients are at risk of SCD from birth, and ICD has a lot of limitations in very young children, the utility of quinidine has to be evaluated further. **Perez Riera AR, Ferreira C, Dubner SJ, Brief review of the recently described short QT syndrome and other cardiac channelopathies. Ann Noninvasive Electrocardiol. 2005; 10:371-377.** Neonates and infant are at risk of SCD, and ICD implant is not feasible in this population.

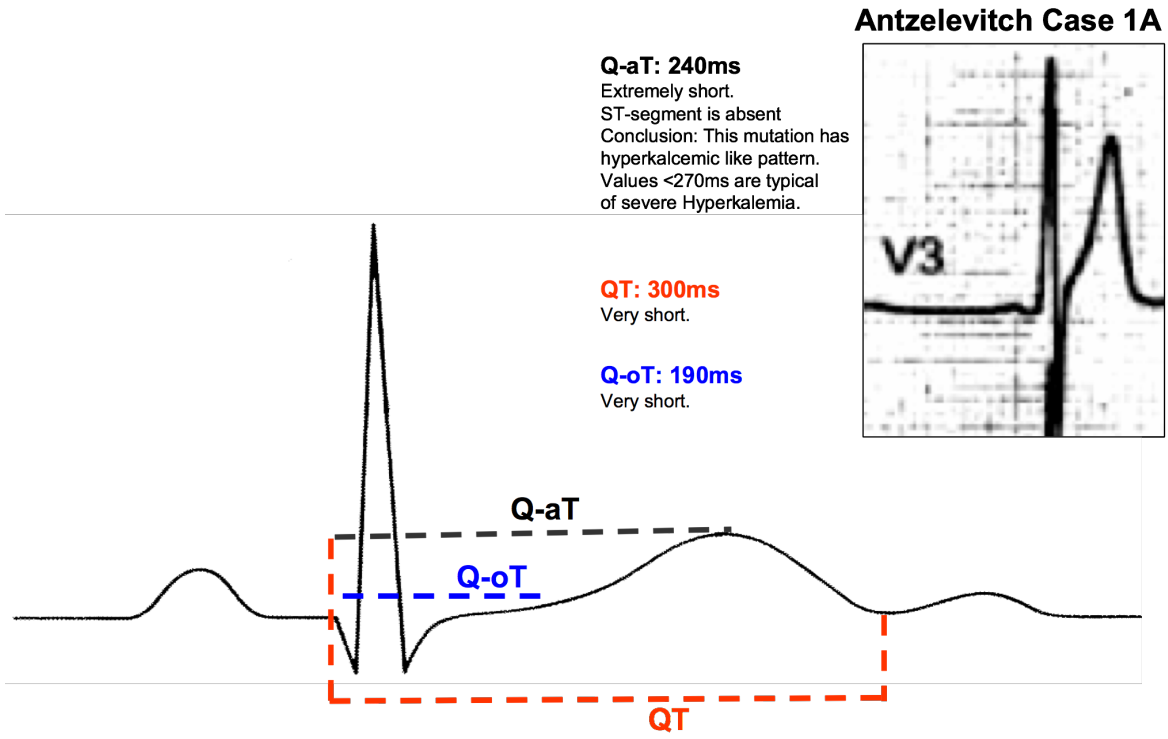
2) **Propaphenone:** Class Ic agent propafenone was effective to prevent episodes of paroxysmal AF in a family with missense mutation (C to G substitution at nucleotide 1764) which resulted in the amino acid change (N588K) in KCNH2 (HERG) gene **Hong K, Bjerregaard P, Gussak I, Short QT syndrome and atrial fibrillation caused by mutation in KCNH2. J Cardiovasc Electrophysiol. 2005;16(4):394-396** In one patients tested by Gaita series Class IC and III antiarrhythmic drugs did not produce a significant QT interval prolongation. **Gaita F, Giustetto C, Bianchi F, Short QT syndrome: pharmacological treatment. J Am Coll Cardiol. 2004; 43:1494-1499.**
3) **Amiodarone** and beta-blocker in association may be helpful in treating episodes of polymorphic VT for patients with an unknown genotype. **Lu LX, Zhou W, Zhang X, et al., Short QT syndrome: a case report and review of literature. Resuscitation. 2006; 71:115-121**

Acquired forms of the SQTS

Several drugs and conditions that induce transient short QT interval, developing acquired forms of the entity. Analogous to the acquired LQTS and acquired Brugada syndrome, SQTS can be induced by acidosis, alteration of the autonomic tone, chronic fatigue syndrome, drugs, electrolyte imbalance and pathophysiologic states. Tables 1 A, B and C show acquired and congenital short QT intervals types .

References

Figure 1



The QT interval can be divided into QoT, QaT, and QeT intervals, which are measured from the beginning of the QRS complex to the origin (**o**), apex (**a**), and the end (e) of the T wave (**QT**), respectively.

Tables 1 A, B and C

A) Hereditary, familiar or congenital SQTS genotypes

SQT1: Ikr or rapid component rectifier K^+ channel

SQT2: Iks slow component rectifier K^+ channel

SQT3: Ik_1 or inward rectifier K^+ current.

B) Mixed phenotype:

Loss-of-function missense mutations of the L-type calcium channel Brugada ECG pattern associated with mild short QT interval.

C) Acquired forms of SQTS

- Acidosis,
- Dysautonomia: Chronic Fatigue Syndrome#
- Drugs: i.e. digoxin intoxication and digoxin effect;

- Electrolyte Imbalance
- Pathophysiologic States.

Chronic fatigue syndrome: Relative short QTc intervals are features of the chronic fatigue syndrome -related dysautonomia. The average supine QTc in chronic fatigue syndrome was 371ms +/- 20ms and QTc on tilt, 385+/-20ms (**Naschitz J, Fields M, Isseroff H, et al. Shortened QT interval: a distinctive feature of the dysautonomia of chronic fatigue syndrome. J Electrocardiol. 2006; 39:389-394.**).