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Congenital Short QT Syndrome

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Congenital short QT syndrome (SQTS) is characterised by extremely short QT intervals, typically with QTc less than 330 ms and a propensity for life threatening ventricular arrhythmias and atrial fibrillation [1-3]. The QT interval in SQTS does not change significantly with heart rate and the T waves have a narrow base and high voltage, similar to those in hyperkalemia [4,5].

Before a diagnosis of SQTS can be considered, intake of drugs like digoxin and hypercalcemia which can shorten the QT interval have to be excluded. Newly introduced antiepiletptic drug rufinamide has the potential to shorten QT interval though clinical adverse effects have not been reported [6]. Shorter QTc intervals have been reported in males with Klinefelter syndrome, which is further aggravated with the administration of testosterone [7].

A recent analysis of 6.4 million electrocardiograms (ECG) from 1.7 million persons recorded between 1995 and 2008 gave a prevalence of short QTc of 0.7 per 100,000 ECGs and 2.7 per 100,000 persons. The cut off for short QTc was 300 ms in this study [8]. There was a 2.6 fold higher risk of death in those with short QTc over an 8.3 year follow up period in this large population based sample.

Analysis of a large hospital based database of 114,334 patients yielded 427 patients with short QT interval [9]. Two of them developed life threatening events on follow up, of which one had additional early repolarization pattern. Prevalence of atrial fibrillation was higher in those with short QT interval than in general population.

In contrast, a study involving 18,825 low risk individuals including athletes documented 0.1% prevalence of QT interval 320 ms or less, with no syncope, sinister family history or mortality [10]. The mean follow up period in this report was 5.3 years.

SQTS was the least common among inherited arrhythmia syndromes, contributing only 1.97% in a European Heart Rhythm Association (EHRA) Survey [11].

Genotype and age of onset

Of the six genotypes, SQT1 has later age of onset in SQT1 (35 +/- 19 years) compared to SQT2 (17 +/- 25 years) and SQT3-6 (19+/-15 years) has been reported by Harrell et al [12]. Villafane J and colleagues [13] identified 4 children in reported series and 2 followed by them with SQTS. All those children who underwent genetic testing had gain of function mutation in KCNQ1 gene, corresponding to SQT2. The authors have documented neonatal atrial fibrillation and bradycardia with SQTS in a subgroup. This subset of children may have persistent bradycardia in utero. Righi D et al [14] has also documented sinus bradycardia with short QT interval at birth which later progressed to junctional bradycardia in infancy and atrial fibrillation with slow ventricular rate in adolescence. This asymptomatic girl had a mutation in KCNQ1 gene and has been followed up for 20 years.

Neurodevelopmental disorders in SQTS

SQTS3 is due to mutations in Kir2.1 channels encoded by the gene KCNJ2. Neurodevelopmental disorders have been associated with cardiac rhythm disorders in SQTS3. Ambrosini E et al [15] noted co-occurrence of short QT interval on ECG and autism-epilepsy phenotype in monozygotic twins. Their findings suggested the need for neuropsychiatric evaluation in patients with SQTS.

Incomplete penetrance

So far it has been thought that SQTS has a high penetrance in that genotype positive, phenotype negative cases are seldom seen [16]. But Harrell DT et al [12] noted that the penetrance was only 82% in their series. Nine of the 51 mutation positive individuals from 16 SQTS families did not have a short QT, but had other abnormalities on ECG like atrial fibrillation.

Altered ventricular function in SQTS

Apart from the propensity for arrhythmias, abnormalities of left ventricular function has also been reported in SQTS. Frea S and colleagues [17] evaluated left ventricular function and mechanical dispersion by tissue Doppler and speckle tracking and tried to correlate with QT interval and genetic mutations. Of the 15 patients studied, 7 had HERG mutations and 3 had KCNQ1 mutations. Mechanical dispersion assessed by tissue Doppler was more in SQTS than in controls and showed an inverse correlation with QT interval. There was also evidence of reduced global longitudinal strain and myocardial performance index.

PQ segment depression in SQTS

The usual causes of PQ segment depression are atrial infarction and pericarditis. But it has also been suggested as a marker of SQTS. In one series, 52 of 64 patients with SQTS (81%) had PQ segment depression [18]. All the nine patients in this series who presented with atrial tachyarrhythmias had PQ segment depression. The authors suggested that PQ segment depression may constitute a novel maker for SQTS.

Role of exercise testing

It is well known that exercise testing has a role in the evaluation of certain cases of long QT syndrome [19]. The role of exercise testing in SQTS was evaluated by Giustetto C et al [Giustetto C 2015]. Twenty one SQTS patients and 20 matched controls underwent an exercise test. SQTS patients showed a reduction in the adaptation of QT interval to heart rate, suggesting that exercise testing could be a useful tool in diagnosing the disease.

Carnitine deficiency and SQTS

Till recently only mutations in cardiac potassium and calcium channel genes have been implicated in SQTS. Three patients with primary systemic carnitine deficiency and SQTS were reported by Roussel J et al [20]. The presenting symptom in one of them was ventricular fibrillation during early adulthood. The authors further created a mouse model of carnitine deficiency by administration of mildronate and demostrated shortening of QT interval which correlated negatively with plasma carnitine concentration. There were associated ventricular tachyarrhythmias coinciding with QT interval shortening.

Natural history of SQTS

Cardiac arrest was the most frequent presenting symptom which occurred in 40% of the probands, with an age range of less than one month to 41 years [16]. In this large cohort of 73 SQTS patients, cardiac arrest occurred at a rate of 4% in the first year of life and 1.3% per year in third to fifth decades. The probability of occurrence of cardiac arrest was 41% within the first four decades of life. Previous history of cardiac arrest was the only predictor of a recurrence at follow up, with a p value of less than 0.0000001. The median follow up was 56 months in 62 patients included in the study.

Risk stratification

After evaluating the data from 61 published cases, Gollob MH et al proposed diagnostic criteria for SQTS in 2011 [21]. Points were allotted to QT inerval with 1 point if if it was lesser than 370 ms and 3 points if less than 330 ms, clinical history of sudden cardiac arrest, documented arrhythmias, unexplained syncope, family history and genotype. High probability of SQTS was considered if there were 4 or more points and low probability if there were only 2 or less number of points. In this scoring at least one point should be scored among the electrocardiographic criteria to obtain additional points from other sections. Points in the clinical history and family history could be considered only once for the scoring.

A modified Gollob Score was published by Villafane J and colleagues in 2013 [22]. The modified Gollob Score did not give points for clinical history and documented arrhythmias while other criteria were retained. As in the Gollob Score points for family history could be received only once in the section.

But in one of the largest single centre natural history study by Mazzanti et al, [16] 5 of the 8 patients who experienced cardiac arrest had a low probability modified Gollob score of 3 or less. Hence the authors urged for caution in using the scoring system for risk stratification.

T wave alternans is considered as a useful risk marker for arrhythmia. But a study involving 13 patients with SQTS found that it was negative in 12 of them [23]. Hence measurement of microvolt T wave alternans using conventional protocol may not be useful as a risk marker in SQTS.

Pharmacotherapy in SQTS

Hydroquinidine was used for long term prophylaxis in 12 of th 53 patients enrolled in the European Short QT registry. It was effective in preventing induction of ventricular arrhythmias as well as prevention of arrhythmic events [24]. It was also noted that those with HERG (SQT1) mutation who had shorter QTc at baseline had a greater prolongation of QTc on treatment with hydoquinidine.

It has been mentioned that combined therapy with potassium channel blockers and beta blockers are

effective in SQTS. But there could be different effects for betablockers in SQT1 and SQT2, at least in experimental situations [25]. Nifekalant, an anti arrhythmic agent being used in Japan produced prolongation of QT interval after intravenous administration in patient with SQTS1. But it is not certain whether this will translate to reduction of the arrhythmic risk in SQTS [26]. Isoprenaline infusion was in successfully managing an electrical storm in patient with SQTS admitted after an aborted sudden cardiac death [27]. Recurrent arrhythmias in SQTS was treated with quinidine in 50%, beta blockers in 19% and isoprenaline infusion in 8% of cases as per the the recent EHRA survey report [11] .

Implantable cardioverter defibillator

Implanatable cardioverter defibrillator (ICD) is definitely indicated in all cases with a history of resuscitated cardiac arrest. In an EHRA survey, 50% of SQTS patients received an ICD while 18% received both ICD and drugs [11].

There is a higher incidence of inappropriate shocks in SQTS because the tall T waves get counted as along with QRS sometimes, leading to a spurious high heart rate as detected by the ICD. The most important predictor of appropriate shocks is a previous history of cardiac arrest.

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