Short QT Syndrome: A Predictable Story

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The classic paper discussed in this essay:

Gussak I, Brugada P, Brugada J, Wright RS, Kopecky SL, Chaitman BR, Bjerregaard P: Idiopathic short QT interval: a new clinical syndrome? *Cardiology* 2000;94:99–102.

Around the end of the last millennium, and some years after the description of the long QT syndrome [1], the familial form of catecholaminergic polymorphic ventricular tachycardia [2] and the Brugada syndrome [3], we continued to be concerned by the occurrence of sudden cardiac death of unknown origin in some patients with a structurally normal heart. Our knowledge of channelopathies had grown exponentially over the previous years and we thought almost everything was known. However, in passionate discussions about the mechanisms of channel dysfunction, the possibility was often considered that some abnormalities in the genes encoding potassium channels might result in a gain of function, and thus accelerate the repolarization process. The resulting disease should be evident on an electrocardiogram (ECG) with a short QT interval. However, until then no one had ever seen such an ECG in patients without electrolytic imbalance, use of a specific drug or extreme heart rate changes. Very interestingly, we had information concerning animals such as rats, mice and especially kangaroos (with an otherwise known high incidence of sudden death) showing a short ECG QT interval (fig. 1) [4].

During the fall of 1999, a lack of success provoked a radical change in our perception of the possible disease

and we moved from theory to a real clinical case. A 37-year-old lady presented with two consecutive episodes of syncope. She was seen on a Friday afternoon in a hospital 100 km south of Barcelona, Spain. An ECG was recorded and forwarded for a second opinion to our Arrhythmia Unit in the Hospital Clinic of Barcelona. The ECG (fig. 3 of the original paper) showed a QTc interval of 248 ms. During a telephone conference a second ECG was requested to evaluate the possibility that the ECG machine was not performing adequately. Using a different machine, a second ECG confirmed the same results. The patient was asked to move to Barcelona for further study but she refused because she had a 6-month-old baby at home and did not want to spend the weekend in the hospital. An appointment was made for the next Monday. Unfortunately, on the Sunday morning the patient died suddenly at home. We then realized that we had encountered our first-ever patient with short QT syndrome (SQTS) that had caused sudden cardiac death. Despite multiple efforts, it was not until almost 5 years later that we could obtain an ECG of the child, which was completely normal.

Some months after the event, the clinical case and the ECG were presented during a discussion about sudden

Fig. 1. ECG of an eastern grey kangaroo [sourced from 22].

Fig. 2. ECG of a patient with SQTs (QTc 270 ms).

cardiac death and repolarization abnormalities involving Josep Brugada, Pedro Brugada, Ihor Gussak and Preben Bjerregaard. The group of Gussak and Bjerregaard immediately reacted and explained their own previously published experience [5] and that of a family with 3 members showing similar ECG characteristics. We decided to put our cases together. This was the origin of the paper entitled 'Idiopathic short QT interval: a new clinical syndrome?', published in *Cardiology* in 2000 [6].

Since then, a very substantial amount of information has become available about the syndrome. More than 200 papers about SQTs have been published in peer-reviewed journals and have had over 1,000 citations.

Probably the most important initial contributions came from the description of the genetic nature of the disease. Identification of three families with several members affected in Italy and Germany allowed description of the first genetic defect, published only 4 years after the initial clinical description of the syndrome [7]. The genetic origin has been reported with an autosomal dominant pattern of inheritance and high penetrance. To date, several mutations related to SQTs have been identified in 6 genes, 3 of them (KCNQ1, KCNJ2 and KCNH2) encoding potassium channels and 3 more (CACNA1C,

CACNB2B and CACNA2D1) encoding calcium channels. Some of them have been associated with patients affected by an overlap of BrS and shortened QT [8–12].

Diagnosis and risk stratification of SQTs has also been the subject of many studies. An expert consensus document endorsed by the principal heart rhythm societies around the world has been recently published on the diagnosis and management of patients with SQTs [13].

Nonetheless, the precise values that define SQTs remain controversial. There is considerable overlap between the QTc intervals of affected and healthy individuals. QTc values below 330 ms are considered diagnostic (fig. 2); values below 350 ms for males and 360 ms for females are considered suspicious in the presence of a pathogenic mutation, a family history or a previous cardiac arrest in the absence of other heart disease.

The risks of ventricular arrhythmias and sudden death have been reported to be high in SQTs [14–20]. Therapeutic recommendations include a class I for ICD implantation in survivors of cardiac arrest and/or in patients with documented spontaneous sustained ventricular tachycardia with or without syncope, and class IIb in asymptomatic patients and a family history of sudden cardiac death.

Some studies have tested the effects of different drugs. To date, quinidine appears the most effective in prolonging the QT interval in patients with SQTs [21], and the expert consensus document also suggests a class IIb indication for quinidine or sotalol in asymptomatic patients with a family history of sudden cardiac death.

Overall, the speed in which the information has accumulated has been spectacular. Less than 4 years separated the clinical description of the first patients and recognition of the first genetic defects responsible for the disease. This is much more efficient in terms of generating knowledge than has been the case with any other cardiac genetic disease, for which decades have sometimes separated disease description and genetic diagnosis. However, in SQTs, clinical information is rather scarce because very few patients and families are identified worldwide. Only very specialized, highly motivated centers are identifying patients. One explanation could be that the disease is highly malignant and patients die before having transmitted the disease to progeny, thus representing a self-extinguishing condition. Other explanations might be related to the need for extensive analysis of ECGs in the population and a clear definition of the QTc limits for diagnosis.

SQTs is a very good example of directed research. Knowledge accumulated over several decades clearly in-

indicated that such a condition must exist. It was just a matter of time before it was recognized in a human. Once this was done, identification of the causes was predictable. The work of many centers has finally resulted in a very substantial amount of information being obtained in a

short period time and using a rather limited number of clinical observations. We are probably moving toward a very efficient way of obtaining relevant information because the basic background is very solid. This could be an example to other areas.

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