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Review

Brugada syndrome: More than 20 years of scientific excitement

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ABSTRACT

In 1992 we reported on eight patients with a particular electrocardiograph (ECG) showing ST segment elevation in the right precordial leads. All patients had a structurally normal heart and had survived one or multiple episodes of near sudden death caused by ventricular fibrillation. We showed 6 years later that this disease, known nowadays as Brugada syndrome, was caused by mutations in the SCN5A gene which encodes for the cardiac sodium channel. Other genes where mutations result in the same ECG have been also identified, with at present more than 17 different genes published. These data show that Brugada syndrome is a genetically heterogeneous disease as is also the case in the long QT syndrome. In Brugada syndrome, the clue to the initial clinical diagnosis remains the abnormal ECG. However, it was evident from the beginning that the ECG of Brugada syndrome is variable and sensitive to many autonomic, drug, exercise, emotions and other external influences such as a meal, fever, changes in heart rate from any cause, and even body position. When followed intensively, all patients with a Brugada ECG will show a completely normal ECG at one or another moment in their lives. The spontaneous normalization of the ECG represents a major diagnostic challenge, because a patient with Brugada syndrome seen during normalization of the ECG may fail to get the correct diagnosis.

In these more than 20 years great challenges have been overcome but some remain, mainly the approach to the asymptomatic individual with a diagnosis of Brugada syndrome. In 30–50% of individuals who die suddenly because of documented or suspected Brugada syndrome, sudden death is the first manifestation of the disease. Thus, these individuals were fully asymptomatic until the first fatal event.

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The start (1992)

In November 1992 an article was published in the *Journal of the American College of Cardiology* (JACC) [1]. Its title was: "Right bundle branch block, persistent ST segment elevation and sudden cardiac death: A distinct clinical and electrocardiographic syndrome. A multicenter report". The study described eight

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patients with a unique electrocardiographic pattern, a structurally normal heart, and a family history of sudden death suggestive of a hereditary disorder. Three of the eight patients were children and two were siblings. The distinct electrocardiographic pattern (Fig. 1) had not been described previously as such in the medical literature. Martini et al. had reported [2] a series of patients with idiopathic ventricular fibrillation and, upon retrospective analysis one had an electrocardiogram with similar characteristics. However, in contrast to the report in JACC, their patients had structural heart disease with no evidence of a hereditary disorder.

The years preceding publication of the JACC article were stimulating and tumultuous. Clinical cardiac electrophysiology was emerging as a subspecialty within cardiology. Since the seminal publications by Coumel et al. [3] and Durrer et al. [4] describing the first applications of programmed electrical stimulation to the human heart, clinical cardiac electrophysiology progressed in the late 1980s and early 1990s beyond esoteric thinking to reach full therapeutic applications in the catheterization laboratory and operating room. The technique of transcoronary chemical ablation was a noble attempt to find a targeted therapy for clinical cardiac arrhythmias [5]. Although successful, this method could never compare to the simplicity of newer methods to come such as radiofrequency and cryo-ablation. Sophisticated cardiac pacemakers became the rule rather than the exception, with innovative features increasingly adding to the physician's armentarium. The implantable cardioverter-defibrillator was becoming an accepted and respected therapy at the dawn of an era when pharmacological therapy for ventricular arrhythmias was disillusioned by the results of the **Cardiac Arrhythmia Suppression Trial** study [6]. With all these "high-tech" advances, the clinical cardiac electrophysiologist increasingly focused on the latest and progressively more sophisticated technical advances. It was, therefore, quite paradoxical that the major breakthrough in characterizing the Brugada syndrome resulted not from high-tech driven research but, rather, an analysis of that old-fashioned paper recording called an electrocardiogram.

The encounter

The weather was unusually pleasant and nice in the morning (1986) in Maastricht, the Netherlands, when, as Director of the Clinical Electrophysiology Laboratory, I received a consultation for a 3-year-old boy while my brother Josep labored at the University of Limburg physiology laboratory deciphering complex double wave re-entrant circuits [7]. Albert Waldo visited Allessie's and discussed the novel concepts of transient and concealed entrainment [8,9]. This academic environment in Maastricht served as a nursery for scientists to be, attracting a cluster of future stars, and producing a multitude of scientific miracles. All electrophysiology Fellows trained became respected cardiologists-electrophysiologists. And later we became respected cardiologists-electrophysiologists that occupied the most prominent positions within their universities.

The excitement could not be greater. Intrigued by the unusual electrocardiographic pattern I showed the electrocardiogram to numerous individuals. It elicited various degrees of interest and disinterest. I kept the electrocardiogram on my desk. Lech had already survived several cardiac arrests, thanks to his father's help who, as a mercenary, was fully trained in cardiopulmonary resuscitation. Eva, Lech's sister, had died suddenly at 3 years of age after several cardiac arrests and in spite of pacemaker implantation and amiodarone therapy. It was only a few months later when Eva's medical records from the University Hospital of Warsaw became available to me. Amazingly, Eva's electrocardiogram was identical to Lech's.

I collected two additional cases of individuals with sudden cardiac death, structurally normal hearts, and the typical electrocardiogram pattern shown in Fig. 1. An abstract with these four patients was presented at the annual meeting of the North American Society of Pacing and Electrophysiology (NASPE) in 1991 [10]. It was accepted as a poster presentation. Josep and I stood by the poster more than the entire allotted time greeting past Fellows from Europe, the USA, and South America. Melvin Scheinmann, who later played a major role in the publication of the 1992 article, passed by. People were fascinated by these four patients and

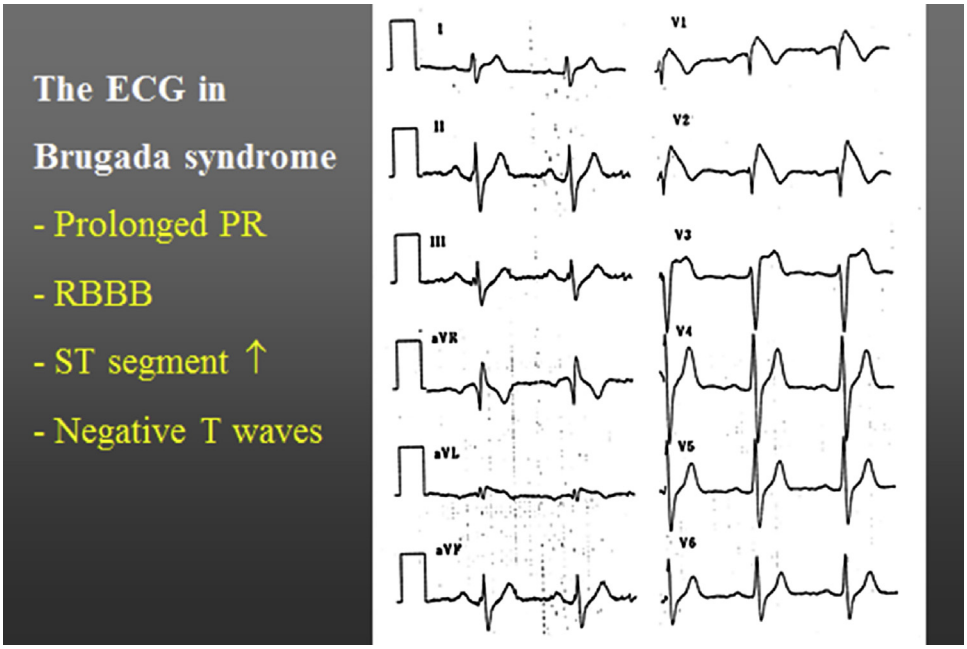

Fig. 1. Typical electrocardiogram (ECG) of Brugada syndrome.
RBBB, right bundle branch block.

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