Editorial Guest

Brugada syndrome; an organic syndrome

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Introduction

The syndrome of right bundle branch block (RBBB), ST-segment elevation and sudden death was first described in 1988 in Italy by Italian doctors from Padua in the *Giornale Italiano di Cardiologia*, [1,2] in *Mises à Jour Cardiologiques* [3] and in the *American Heart Journal* [4]. This syndrome is now known worldwide as the "Brugada syndrome", reflecting the name of those who described later the same entity in 1992 [5]. At present, more than 1000 papers on this syndrome are reported in the Medline. In more than 20% of cases (including all the patients submitted to a necropsy study), some form of organic heart disease has been increasingly recognized, mainly of the right ventricle, while in the vast majority of patients a structural abnormality has not yet been identified. This may be due to the fact that the investigation was incomplete as right ventricular angiography, endomyocardial biopsy and magnetic resonance imaging were not frequently utilized for the diagnosis.

The limited approach to the syndrome, only devoted to the imaging of the ECG than to its structural basis, has led to two different theories on the pathophysiology of the syndrome: the first, which we have confimed in the last two decades, relates to the precordial ECG and a depolarization abnormality due to an organic heart disease, whereas the second and most popular, ascribes the syndrome to a functional abnormality of repolarization(http://digilander.libero.it/martini_syndrome).

Historical Notes

In 1953, Osher and Wolff [6] reported a dynamic ECG abnormality, simulating an acute myocardial infarction, in a healthy man. It is of interest that they wrote what we are still discussing: "This is apparently due to prolongation of the depolarization process by right bundle block or possibly focal block with delayed activation of a portion of the right ventricle: unusually early onset of repolarization may also play a role". A similar ECG pattern, this time associated with an abortive sudden death occurred in Padua, Italy in a living 42-year-old male while talking with a post officer on the 2nd of October 1984.

A new "syndrome" characterized by a clinical event (in an abortive sudden death) associated with the abnormal ECG findings, was first

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presented at the National Congress of Italian Cardiologists, held in Florence, by Nava, Martini, Thiene and colleagues, working in Padua with Professor Sergio Dalla Volta in 1988[1,2]. Shortly after, Nava et al. [3] published the first ECG which is considered worldwide as the typical ECG of the syndrome, and which is now called the "Brugada sign". One year later, a full description of the syndrome was published in the *American Heart Journal*[4]. It is noteworthy that in our paper we did not re-publish only "the typical" , but most of the ECG variations of the syndrome, namely dynamic or isolated ST-segment abnormalities, incomplete or complete RBBB, sometimes associated with an atrioventricular and fascicular conduction impairment, and a prolonged HV interval. An extended PR interval, left axis deviation, some incomplete RBBB and minor ST-segment elevation were present in patient 4 of our paper. The same patient was re-introduced by Corrado et al.[7], and that ECG was an excellent example of the dynamic pattern sometimes observed in this syndrome. Despite the typical functional ECG pattern (highly prevalent also in his siblings), this patient had anatomical evidence of a right ventricular cardiomyopathy. In the same paper, a complete RBBB morphology was present in patient 1, with only a slight ST-segment elevation in V1 and V2. Isolated slight ST/T anomalies/elevation as seen in patients 2 and 5 of our paper may very well have been a potential marker of the syndrome, but drug testing was not performed at that time. The presence of late potentials, corresponding to ST-segment elevation, was proven both by intra-cavitary recordings[3] and by signal-averaged ECG[8]. The second description of the syndrome was presented by Aihara et al.[9] in patients without apparent heart disease, and the third by the Brugada brothers[10], five years after the initial Italian description. Further improvements in the evidence-based knowledge of this syndrome came from Naccarella[11] who demonstrated that the typical ECG may occasionally be recorded at a higher precordial level, by Brugada et al.[10] who introduced the class 1C drug challenge and by Chen et al,[12] who reported the first genetic abnormalities[5]. A major advance was reported by Haissaguerre et al.[13], who introduced a possible major step forwards in the cure of this syndrome: the ablation therapy.

In the last years an increasing number of papers confirm the presence of structural heart abnormalities at the right ventricular outflow tract level, as well as an underlying depolarization abnormality. After two decades of heavy debate the initial theories are more and more re-discovered or acknowledged.

What is the syndrome?

The syndrome of RBBB, ST-segment elevation and sudden death must be distinguished from the simple presence of a similar ECG in a healthy individual, to avoid the overestimation of the disease and its unnecessary treatment. The true syndrome is characterized by:

1-ECG patterns with different degrees of RBBB and sometimes left axis deviation and a prolonged PR interval. The most typical ECG shows an r1 pattern in V1 (the so-called J wave)[3], followed by a coved ST segment (type 1 ECG pattern). A saddle back ST elevation of different degree, has also been described in the syndrome (type 2 and 3 ECG pattern)[14]. The pattern of ST-segment elevation in V1-V3 (type 1-3) may vary in different observations: this is the so called dynamic pattern, claimed, but not proved to be the evidence of a

functional phenomenon. This pattern may be elicited by by fever, antidepressant medication, cocaine, ionic changes, hyperglycemia, and by different antiarrhythmic drugs including flecainide, ajmaline, procainamide, disopyramide, propafenone, pilsicainide, amiodarone.

2- Prolonged HV interval, mainly in cases with major conduction abnormalities, and sometime with a positive SCN5A genetic study[15].

3- Frequent positive late potentials (70%) at signal-averaged ECG. Late potentials may also be recorded at the right ventricular outflow tract (RVOT) level during endocavitary recording, at body surface mapping and at direct epicardial recordings[3,8,16-18]. As a rule, they can be recorded after flecainide challenge[17,19], demonstrating that this drug could induce a late depolarization rather than an early repolarization abnormality. Late potentials usually indicate organic heart disease, even though they may occur in subjects without an evident cardiomyopathy. Antzelevitch has proposed a theory called the second upstroke of the epicardial action potential, thought to be so greatly accentuated in the Brugada syndrome that might be capable of generating late potentials when RVOT activation is otherwise normal. This experimental theory has not been confirmed[18].

4- The prevalence of the syndrome has also been debated. In the first consensus conference[14] the prevalence of the syndrome was reported to range from 5 to 66 cases/10000 inhabitants which was the same as that of HIV infection[20]. In a recent review[21] this prevalence was reduced to 1-5 /10000 inhabitants, which is still a high rate. As a personal experience in my area of 186.000 inhabitants, not a single case of sudden death linked to the syndrome during last decade. The problem should be somehow different in Asia where the unexplained nocturnal sudden death syndrome (Pokkurry death, Bangucut disease) could occur in young males. The data are however controversial, as the syndrome was often confused with the isolated ECG pattern.

The type 1 ECG may be encountered in not more than 0.016% healthy Europeans whereas type 2 and 3 are present in 0.04-0.6% healthy individuals, mostly males[22,23]. In South east Asia the prevalence seemed to be higher, but there was incearsing bias in these series due to the misleading popular classification in three ECG patterns. Type 2 and type 3 of this classification were no longer retained to be a typical clue to the syndrome[24], unless a spontaneous type 1 pattern was also recorded in these individuals According to recent reviewers, the mortality of asymptomatic subjects occasionally observed in the ECG seemed to be much lower than 0.3% per year[25].

5- 1 C drug challenge[11]. It has been shown that the intravenous administration of the class 1C antiarrhythmic agents, particularly ajmaline and flecainide, may unmask the presence of the ECG pattern in patients affected by the syndrome. Brugada initially described a 100% correlation between SCN5A (a gene on chromosome 3) carriers and the spontaneous or drug inducible ECG pattern[25]. This assumption was not confirmed by others, and was recently re-discussed. Priori et al.[26,27] demonstrated that the test may be negative in as many as 80% of asymptomatic gene carriers. It is also debated whether these drugs were specific for the syndrome, as normal subjects and patients with right ventricular cardiomyopathy might show similar ECG changes[28]. At present time the popular use of type 1 C drugs such as flecainide, ajmaline, procainamide, disopyramide, propafenone, and pilsicainide for identifying

patients at risk is uncertain. Drug-induced conversion of Type 3 to Type 2 ST-segment elevation is now considered inconclusive for diagnosis and risk stratification of Brugada syndrome.

6- Male predominance (up to 85%), and familial involvement (autosomal dominant with variable expression)[29]; Several mutations of SCN5A have been proposed, as the pathophysiological explanation of the syndrome. A 50% prevalence of this finding was initially described[12]. The syndrome is currently classified among the channellopathies, but it has been admitted in the recent consensus[14] that SCN5A gene abnormalities may not be found, in the vast majority of patients, as Antzelevitch has recently reported only a 15% prevalence[21]. Interestingly these abnormalities were not found in some high risk groups[30], which raised some questions on its real prevalence, and on the *in vitro* expression of such genetic defects which could not explain the link with the clinical phenotype. SCN5A gene abnormalities are so frequent, and have also been described in the long QT syndrome, atrio-ventricular block, in sick sinus syndrome, atrial fibrillation, and in myocardial infarction. A study has claimed that such abnormalities are widespread in some populations[31].

Other genetic abnormalities of the calcium channels, the ankirin system, and of Glycerol-3-Phosphate Dehydrogenase 1 like Gene (GPD1-L), have recently been documented, but their significance needs further studies[32-32].

However, these mutations, in any case, do not exclude a coexistent structural heart disease as found in our first patient, who was submitted to necropsy study described in our initial report. This patients had a familial right ventricular cardiomyopathy and and SCN5A abnormalities[4].

7- High recurrence rate of both spontaneous and induced ventricular fibrillation. The lethal arrhythmia may be easily induced both in patients and in asymptomatic subjects mainly with type 1 ECG, which raises problems on the specificity and predictive accuracy of invasive electrical stimulation. There is much concern in favor of these healthy asymptomatic subjects, as most of them underwent implantation of a defibrillator because of easily inducible ventricular fibrillation at electrophysiologic study, with devasting consequences[35]. With regard to the risk stratification of these subjects, long-term data on the predictive accuracy of this approach are heavily debated. Recently some leading authorities no longer accept the concept that asymptomatic subjects with this ECG should be submitted to invasive cardiac stimulations and if positive implanted with an ICD [36-38].

8- The fatal event (when recorded), is characterized by polymorphic ventricular tachycardia, which degenerated into ventricular fibrillation. Some patients have episodes of ventricular tachycardia of left bundle branch block morphology[39].

9- The autonomic tone (particularly the enhanced vagal tone), plays a role in this syndrome, and may be responsible for the dynamic pattern of the ECG, as well as sudden death which may also occur during the night (especially in Asians)[40]. Patients with clear organic heart disease may also share a dynamic pattern, but its association with the autonomic tone was less clear.

10- Long term prognosis is a highly and fiercely debated topic in recent medical studies[36]. Currently, males with a type 1

ECG and previous cardiac arrest or unexplained syncope are at risk and must be treated with an ICD. For other subjects (especially the asymptomatic cases having the discussed ECG, even if they belonged to an affected family) there are no data which could clearly support the evidence for an aggressive approach[41].

11- Laboratory data on this disease have limited evidence-based clinical correlation. At present not a single serum abnormality has been associated with the syndrome at present time. Experimental data, obtained by wedge preparations were of limited value. The J wave (Osborn wave), as seen in the left precordial leads in conditions of cold temperature and vagotonia, was studied by elegant experiments of Yan and Antzelevitch[42,43]. They demonstrated that this wave was induced in the left ventricle by an Ito (ionic current) abnormality. They also provided laboratory evidence on a wedge preparation, that supported the hypothesis of an heterogeneous distribution of a spike-and-dome morphology of the action potential across the ventricular wall that could underlie the ECG pattern, as well as the reentry circuit.

These elegant hypotheses are far from being confirmed. It is difficult to translate a wedge study on the clinical ground[44], and the recent study by Coronel on an explanted heart failed to demonstrate any functional defect and confirmed a structural abnormality in the heart discussed and a conduction delay of the right ventricular outflow tract[45].

Is the syndrome a functional or organic entity?

As we demonstrated in our initial description of the "so called Brugada syndrome[1-4]" (http://digilander.libero.it/martini_syndrome), there is frequent and increasing evidence, after detailed examination (including necropsy in rare cases), of some form of latent organic heart disease, particularly of the right ventricle underlying the syndrome[45-65]. These abnormalities are characterized by lesions within the main conduction system (His and right bundle branch) and atrophy, fibrosis, adiposis of the right ventricular wall, especially of the right ventricular outflow tract. These abnormalities may be difficult to assess, especially if the cardiologist is more interested in electrophysiology than in clinical and morphologic investigation of subtle abnormalities. Also the consensus conference on this disease, has stated that no definite line could be drawn between functional and organic disease. Also Brugada has recently described in detail a severe structural heart disease underlying the syndrome and its electrocardiographic patterns of conduction delay[45].

To our knowledge, a normal heart underlying the syndrome has not yet been demonstrated at autopsy. None of the references available in the Brugada website (http://www.brugada.org), or in Medline describes in detail a normal autopsy case. Moreover some patients, with initial diagnosis of a normal heart, had subsequent evidence of structural heart disease[60], much similar to right ventricular dysplasia/cardiomyopathy. It must be affirmed, however, that the genetic abnormality currently encountered in right ventricular dysplasia were not found in the syndrome. A right ventricular structural heart disease was demonstrated by different authors at necropsy, angiography, magnetic resonance studies and again by endomyocardial biopsies which were recently found to be abnormal in all patients by Frustaci[65].

Despite such increasing number of evidence

-based clinical and investigational data supporting the organic theory, it must be clearly affirmed that this has not yet provided a solution to the problem. Many more data on the histological pattern, the true genetic abnormality, the role of the autonomic tone, the significance of the ECG patterns, and the risk stratification are an ongoing process which will accupy the minds of many scientists for next decade. We thus, in the near future, hope for well-controlled and sustained scientific studies, including humble but delineated case reports along with relevant theories and guidelines, rather than astonishing but transient discoveries.

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