REVIEW ARTICLE

Brugada Syndrome: A Major Cause of Sudden Cardiac Death

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ABSTRACT

In 1992 a new syndrome was described consisting of syncopal episodes or sudden death in patients with a structurally normal heart and an electrocardiogram characteristic of right bundle branch block with ST segment elevation in leads V1 to V3. Brugada syndrome is an autosomal dominant disorder. It has been shown to be associated with mutations in the gene (SCN5A) that encodes for the sodium ion channel in cardiac myocyte. Over 160 mutations of gene SCN5A have been identified. The incidence of the disease is difficult to estimate, but it causes sudden deaths of 5 per 10,000 inhabitants per year and involved much more frequently in people of Asian ancestry. Diagnosis can be easily made by means of genetic analysis and ECG. Recent data suggest that loss of the action potential dome in the right ventricular epicardium underlies ST segment elevation seen in this syndrome. Right ventricular epicardium is preferentially affected because of the predominance of transient outward current in this tissue. Antiarrhythmic drugs like amiodarone and beta-blockers do not prevent death in symptomatic or asymptomatic individuals. Though Implantation of an automatic cardioverter–defibrillator is the only recently proven effective therapy; Quinidine has been found to decrease Ventricular fibrillation and could prove to be a secured option of implantable cardioverter–defibrillator. However, researcher set focus on gene therapy that may offer an enduring cure in future years. The purpose of this brief review is to record the past highlights that have brought us to our present understanding of Brugada syndrome.

Keywords: Brugada syndrome, Sudden cardiac death, Ventricular arrhythmias

INTRODUCTION

Brugada syndrome (BS) is a condition that causes a disruption of the heart's normal rhythm. Specifically, this disorder can lead to uncoordinated electrical activity in the heart's lower chambers (ventricles), an abnormality called ventricular tachycardia (VT) or ventricular fibrillation (VF) leading to sudden cardiac dearth.[1] The Brugada syndrome is a genetic disease[2] that causes sudden unexplained death syndrome (SUDS),[1,2] also known as sudden adult death syndrome (SADS), and is the most common cause of unpredicted death in young men without known underlying cardiac diseases.[1,3,4] If untreated, the irregular heartbeats can cause fainting (syncope),[5] seizures, difficulty in breathing, or sudden death.[6]

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Brugada syndrome usually becomes apparent in adulthood, with a mean age of sudden death of approximately 40 years.[7] But the signs and the symptoms, including sudden death, can occur any time from early infancy to old age. The youngest patient diagnosed with the syndrome was 2 days of age only, and the oldest one was 84 years.[7]

Though Brugada syndrome was first discovered in 1992, as a primary electrical disorders that, characteristically, are not associated with concomitant structural cardiac abnormalities,[4,8] but this concept has been challenged now-a-days.[9] Subtle structural abnormalities in the right ventricular outflow tract have been reported by Frustaci A et al (2005)[9]. The Brugada syndrome has gained wide recognition throughout the world and today it is believed to be responsible for 4% to 12% of all sudden deaths and approximately 20% of deaths in patients with structurally normal hearts.[4,7,10] The incidence of the disease is on the order of 5 per 10,000 inhabitants and, apart from accidents, is the leading cause of death of men under the age of 50 in regions of the world where the inherited syndrome is endemic.[7,10]

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Interestingly it was reported by many researcher that, Brugada syndrome occurs much more frequently in people of Asian ancestry, particularly in Japanese and Southeast Asian populations.[1,8,10.11]

Although Brugada syndrome affects both men and women, the condition appears to be 8 to 10 times more common in men. Researchers suspect that testosterone, a sex hormone present at much higher levels in men, may be responsible for this difference.[12]

Inheritance of Brugada Syndrome

The Brugada syndrome is an autosomal dominant disease with incomplete penetrance that may cause syncope and sudden cardiac death in young individuals.[7,11,13] It means one copy of the altered gene in each cell is sufficient to cause the disorder. In most cases, an affected person has one parent with this condition. Other cases may result from new mutations in the gene. These cases occur in people with no history of the disorder in their family.

Genetic Basis of Brugada Syndrome

Approximately 20 – 30% of the cases of Brugada syndrome have been shown to be associated with mutations in the gene that encodes for the sodium ion channel in the cell membranes of the muscle cells of the heart (the cardiac myocytes).[6,13,14] The gene, named SCN5A, is located on the short arm of the third chromosome (3p21).[13-16] Though several pathogenic genes have been identified till date as associated with the disease, but *SCN5A* is the most prevalent one.[17]

Mutations in the *SCN5A* gene have been identified in less than one-third of people with Brugada syndrome.[13] This gene gives instructions for building a sodium channel, which normally transports positively charged sodium ions into cardiac myocytes. This type of ion channel plays a vital role in preserving the normal cardiac rhythm. Mutations in the *SCN5A* gene modify the organization or purpose of the channel, which lower the flow of sodium ions into cells. An interruption in ion transport alters the mode of the heart beats, leading to the abnormal heart rhythm known as VF.[13,15,18,19]

In the Brugada syndrome, mutations in SCN5A reduce sodium current density, causing premature repolarization of the epicardial action potential due to an all or none repolarization at the end of phase-1. The loss of the action potential dome in epicardium, but not endocardium, creates a dispersion of repolarization across the ventricular wall,[20] resulting in a transmural voltage gradient that manifests in the electrocardiogram (ECG) as an ST-segment elevation and in the development of a vulnerable window during which reentry can be induced. Under these conditions, loss of the action potential dome at some epicardial sites but not others gives rise to phase 2 reentries, which provides an extra systole capable of precipitating ventricular tachycardia/ventricular fibrillation.[20]

Data collected from a multi-center study performing a complete genetic analysis of SCN5A, revealed that in 37% cases, the disease was familial, whereas in the majority it was sporadic (63%).[21] Five novel SCN5A mutations (2602delC, resulting in: E867X; 2581_2582del TT: F861fs951X; 2673G>A: E1225K; 4435_4437delAAG: K1479del; and 5425C>A: S1812X) were found and randomly located in SCN5A. Mutation frequencies (SCN5A+) differed significantly between familial (38%) and sporadic disease (0%) (p=0.001).[21]

Over 160 mutations in the SCN5A gene have been discovered to date, each having varying mechanisms and effects on function, thereby explaining the varying degrees of penetration and expression of this disorder.[22]

An example of one of the mechanisms in which a loss of function of the sodium channel occurs is a mutation in the gene that disrupts the sodium channel's ability to bind properly to ankyrin-G, an important protein mediating interaction between ion channels and cytoskeletal elements.[23] Very recently a mutation in a second gene, Glycerol-3-phosphate dehydrogenase 1-like gene (*GPD1L*) has been shown to result in Brugada syndrome in a large multigenerational family (London, 2006).[23] This gene acts as an ion channel modulator in the heart, although the exact mechanism is not yet well understood.[24]

Recently Antzelevitch has identified mutations in the L-type calcium channel subunits *CACNA1C* (A39V and G490R) and *CACNB2* (S481L) leading to ST elevation and a relatively short QT interval (below 360 ms).[14,25]

In affected people without an identified *SCN5A* mutation, the cause of Brugada syndrome is often unknown. In some cases, certain drugs may cause a nongenetic (acquired) form of the disorder.[26] Drugs that can induce an altered heart rhythm and therefore can mimic Brugada ECG pattern includes class IA (ajmaline) or class 1C (flecainide) antiarrhythmic drug, beta-blockers and nitrates, tricyclic antidepressants and lithium, first-generation antihistamines, calcium channel blockers like verapamil, anesthetic agents like Propofol and Bupivacaine etc.[26] Abnormally high blood levels of calcium (hypercalcemia) or potassium (hyperkalemia), as well as unusually low potassium levels (hypokalemia) also have been associated with acquired Brugada syndrome. In addition to causing a nongenetic form of this disorder, these factors may trigger symptoms in people with an underlying *SCN5A* mutation.[26]

Pathophysiology

There are lots of passionate debates regarding the pathophysiology of Brugada syndrome. Despite 20 years of advancement, the pathophysiology of Brugada syndrome has become progressively more complex. It has been suggested that a number of disease processes may lead to the Brugada ECG, which is not as specific as once thought.[27]

Mutations in genes encoding components of the sodium (most common), calcium and potassium channels have been found to be associated with the Brugada syndrome, but evidence of direct causation is often lacking and therefore, cannot explain the phenotype of this syndrome without doubt. It is postulated that a number of modulating factors have also emerged, that may influence the Brugada syndrome phenotype. These include genetic modifiers, drugs, gender and imbalance in autonomic tone etc. It is possible that genetic susceptibility in combination with these modulating factors acquired or otherwise, may lead to the Brugada phenotype.[28] Therefore, though clinical evidence suggest that genetic background may play a powerful role in the pathophysiology of Brugada syndrome; but other factors beyond mutant sodium channels that produce reduced sodium current should be kept in mind.

Diagnosis of Brugada Syndrome

Clarification of the genetic substrates underlying heritable cardiac arrhythmia syndromes has uncovered new arrhythmogenic mechanisms and given rise to a number of clinically meaningful genotype-phenotype correlations. As such, genetic testing for these disorders now carries important diagnostic, prognostic, and therapeutic implications.[29]

Genetic testing for Brugada syndrome is clinically available and may help confirms a diagnosis as well as differentiates between relatives who are at risk for the disease and those who are not.[29]

Other tool for the diagnosis is ECG. With an electrocardiographic pattern typical of ST segment elevation in leads V1–V3 [30] with or without right bundle branch block is characteristic of Brugada syndrome.[11,31,32]

Electrocardiography

According to a recent consensus document, type 1 ST segment elevation either spontaneously present or induced with Ajmaline/Flecainide test is considered diagnostic. Type 1 and 2 may lead to suspicion but drug challenge is required for diagnosis.[11]

In some cases, the disease can be detected by observing characteristic patterns on an electrocardiogram, which may be present all the time or might be elicited by the administration of particular drugs e.g. Class IA (ajmaline) or class 1C (flecainide) antiarrhythmic drugs that block sodium channels and cause appearance of ECG abnormalities or resurface spontaneously due to as yet unclarified triggers.

In Figure 1 normal ECG patterns are shown in lead v_1-v_3 to compare three different ECG patterns of Brugada syndrome in the same leads[7,33,34] as shown in Figure 2:

1. Type 1 has a coved type ST elevation with at least 2 mm (0.2 mV) J-point elevation a gradually descending ST segment followed by a negative T-wave.
2. Type 2 has a saddle back pattern with a least 2 mm J-point elevation and at least 1 mm ST elevation with a positive or biphasic T-wave. Type 2 pattern can occasionally be seen in healthy subjects.
3. Type 3 has either a coved (type 1 like) or a saddle back (type 2 like) pattern with less than 2 mm J-point elevation and less than 1 mm ST elevation. Type 3 pattern is not uncommon in healthy subjects.

The mechanisms responsible for ST segment elevation and the genesis of VT/VF in the Brugada syndrome are slowly coming into better focus. The available data suggest that a down sloping ST segment elevation observed in the right precordial leads of patients afflicted with the Brugada syndrome is the result of depression or loss of the action potential dome in right ventricular epicardium.[35,36]

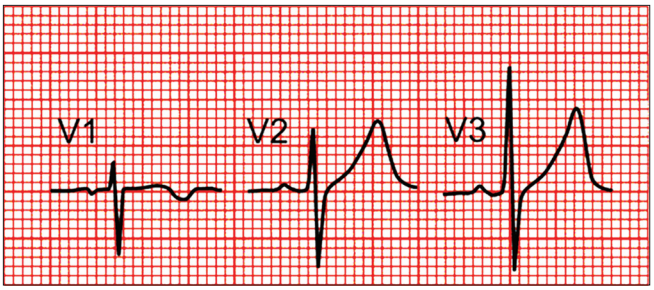

Figure 1: Normal ECG pattern in lead v1-v3

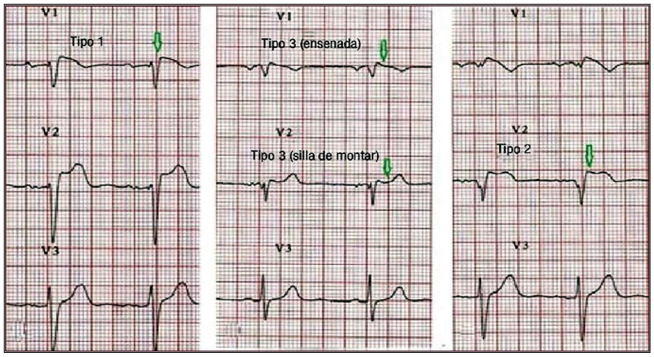

Figure 2: Different types of ECG pattern in Brugada syndrome

Correlation of Brugada Syndrome with other Syndromes and the Pseudo-syndrome

It is very interesting to note that, there are some diseases which may result in ECG manifestations similar to the Brugada syndrome. For instance, in patients with Chagas' disease, Chiale et al. showed that the intravenous administration of ajmaline has uncovered latent conduction disturbances that mimics Brugada syndrome.[11,37] Ventricular arrhythmias were observed in 8% of patients and in 7% cases elevation of the ST segment in the right precordial leads were recorded.[11,37] Hence, the question arises of the relationship between Chagas' disease and Brugada syndrome in these patients.[11] Other conditions may result in ECGs simulating Brugada syndrome: Steinert's disease, pectus excavatum, and mediastinal tumours.[11] Therefore, these should be excluded before diagnosing Brugada syndrome.

Treatment

The cause of death in Brugada syndrome is fast polymorphic VT or VF and unfortunately these arrhythmias appear with no warning. Because antiarrhythmic drugs (like amiodarone or beta-blockers) do not protect against sudden cardiac death,[37] the only available treatment is the implantable cardioverter–defibrillator (ICD).[4,5,11,13] This device effectively recognizes and treats the ventricular arrhythmias in Brugada syndrome. This continuously monitors the heart rhythm and will defibrillate an individual if VF is noted. The prognosis of ICD in Brugada syndrome is good and total mortality in patients with the Brugada syndrome has been 0% with up to 10 years follow-up.[11] But the ideal candidates for ICD in Brugada syndrome are: They should be usually symptomatic with no coronary artery disease or any other diseases.[11]

On the other hand, major concerns arise in the treatment of asymptomatic individuals. Data from electrophysiological investigations did not provide any help to predict prognosis, although this may be caused by a type II error (an insufficient number of patients to prove a statistically significant difference).[11]

At present, four different groups of patients with Brugada syndrome can be distinguished.[7,11,20]

1. Symptomatic individuals with the disease require an ICD
2. Asymptomatic patients with a family history of sudden death, and inducible polymorphic VT or ventricular fibrillation who also require an ICD
3. Asymptomatic individuals, who have no family history of sudden death but also show inducible sustained polymorphic ventricular arrhythmias, also require a ICD; and
4. Asymptomatic individuals without a family history of sudden death and no inducible ventricular arrhythmias should not be treated with ICD but followed-up carefully for development of symptoms suggesting arrhythmias (particularly syncope).

However, that these recommendations may be rapidly changed depending upon the availability of new data. The results of the many studies showed that, ICD implantation might be unnecessary for the vast majority of patients. On the other hand, 28%[38] to 32%[39] of these young individuals develop very serious complications directly related to ICD implantation. Therefore, It is not surprising that the complication rate after ICD implantation for Brugada syndrome is higher than the antiarrhythmic therapy as stated by Sacher F et al and Kron J et al.[38, 40]

It is interesting to note here that, few recent studies have evaluated the role of quinidine, a Class Ia antiarrhythmic drug, for decreasing VF episodes occurring in this syndrome. Quinidine has been found to both decrease the number of VF episodes and correct spontaneous ECG changes, possibly via inhibiting I_{to} channels.[41-43] Nonrandomized studies propose that, quinidine prevents spontaneous arrhythmias in high-risk patients with Brugada syndrome during long-term follow-up.[44] Those studies recommended that, suppression of spontaneous arrhythmias by quinidine could prove to be a safe alternative to automatic implantable cardioverter-defibrillator (ICD) therapy for a substantial proportion of patients with Brugada syndrome.[41,43] Among survivors of VF or sustained VT causing severe symptoms, the implantable cardioverter-defibrillator is superior to antiarrhythmic drugs for increasing overall survival as reported by some researchers.[45] However, randomized studies comparing these two therapies appear necessary.

Risk Stratification

Risk stratification is currently guided by clinical and ECG features with the asymptomatic patient posing a particular challenge. The use of programmed electrical stimulation is controversial with the majority of evidence suggesting a poor positive predictive value, but may still have reasonable negative predictive value. There are several emerging risk markers like syncope, family history of sudden death and positive electrophysiological study (EPS) that may prove of use but need prospective validation.[46]

Individuals with type 1 Brugada ECG pattern may suffer from malignant ventricular arrhythmias (Brugada syndrome). Patients with Brugada syndrome and documented cardiac arrest should receive an ICD. In the remaining subjects, the best management is controversial. Many data suggest that patients with syncope, particularly if they have a spontaneous type 1 ECG pattern, have a significant risk. In the remaining population of asymptomatic subjects, the risk is lower but not insignificant. How to manage these

latter cases is an unsettled issue. The usefulness of the EPS in risk stratification, i.e. inducibility of sustained ventricular tachycardia/fibrillation, is also controversial. Indeed, some authors strongly support the prognostic value of EPS, while others completely deny its usefulness.[47]

It is easy to recommend an ICD to a patient who has just survived a cardiac arrest, but what advice should be given to his asymptomatic brother who might have the same genetic disease? In this age of gene testing and sophisticated technology, such questions arise frequently, and the answers are complex. All the researchers sound a word of caution with their findings due to the short follow-up in their studies. Whether initially asymptomatic patients could have a cardiac arrest decade after their diagnosis is unknown. Such findings will only be revealed eventually. Affected family members who have not yet had symptoms must wait until complete detection of the natural history of Brugada syndrome. All together, risk stratification, particularly in asymptomatic patients with Brugada syndrome are distracted. Future studies with uniform design and long-term follow-up are needed.

Prognosis

This syndrome has a very unfortunate prediction when left untreated: One third of patients who suffer syncopal episodes, or who are resuscitated from near-sudden death develop further episodes of polymorphic VT within two years.[48] Unluckily, the prognosis of asymptomatic individuals with a typical ECG is also poor. In spite of not having any earlier symptoms, one third of these individuals also present a first polymorphic VT or VF within two years of follow-up.[49]

Future perspectives

Two decades of extensive research on Brugada syndrome has revealed parts of its genetic background and electrophysiological and clinical characteristics. Queries remain unclear regarding the method that plays the fundamental role of the disease. The actual role of its genetic background, including polymorphisms; and other confounding factors need more explanation. Further enhanced exploration will be needed to discover the answer of this questions.[50]

CONCLUSION

The Brugada syndrome is a distinct form of idiopathic ventricular fibrillation and may cause sudden cardiac death in healthy young individuals. It has grown wide detection throughout the world and today is believed to be responsible for considerable amount of sudden deaths with structurally normal hearts. At present, sudden death can only be prevented by implanting a cardioverter–defibrillator (ICD); however, Quinidine effectively prevents VF induction in patients with Brugada syndrome and can suppresses spontaneous arrhythmias and could prove to be a safe alternative to automatic implantable cardioverter-defibrillator therapy for a substantial proportion of patients with Brugada syndrome. But yet randomized studies comparing these two therapies seem warranted. As the Brugada syndrome is mostly genetically determined, definitely gene therapy may recommend a new tool to cure in near future.

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