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BRUGADA SYNDROME: AN OVERVIEW

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ABSTRACT
Brugada syndrome is an uncommon heart arrhythmic disease defined by sustained ST-segment elevation in the right pericardial leads and electrocardiographic right bundle branch block. It's linked to ventricular fibrillation and an increased risk of sudden cardiac death, especially in young men with structurally normal hearts. Patients with idiopathic ventricular fibrillation, self-terminating polymorphic ventricular tachycardia, a family history of sudden cardiac death in a child, and/or syncope with the distinctive electrocardiography (ECG) abnormalities should be suspected of the condition. Characterization of the RVOT's unique morphology and electrophysiology during the last few decades has shown the RVOT's arrhythmogenic characteristics. Despite recent insights from large population cohorts, risk classification among impacted patients remains a difficulty. The major therapy in Brugada syndrome is implantable cardiac defibrillators, which are linked with a high rate of problems. The key challenge is risk assessment of individuals with Brugada syndrome.

KEYWORDS: Brugada syndrome, Arrhythmia, Genetic mutation, Defribrillator, Right ventricular outflow tract (rvot).

INTRODUCTION
Brugada syndrome is an uncommon cardiac arrhythmia characterised by prolonged ST-segment elevation in the right precordial leads and electrocardiographic right bundle branch block. It's linked to ventricular fibrillation and an increased risk of sudden cardiac death, especially in young men with structurally normal hearts. Electrocardiographic patterns can emerge spontaneously or after pharmaceutical stimulation, and patients can remain asymptomatic. Brugada syndrome (BrS) was first reported 20 years ago as a unique clinical entity with a characteristic electrocardiographic (ECG) pattern (right bundle branch block and prolonged ST-segment elevation in right precordial leads) and a substantial risk of sudden cardiac death.The symptoms normally occur around the age of 40, but children as young as one year old have been reported to be affected. Because of the influence of hormones and the gender distribution of ion channels across the heart, males are more likely to be symptomatic than females.[1] Brugada syndrome is linked to a number of different genetic mutations. These mutations mostly impact genes that code for subunits of cardiac sodium, calcium, and potassium channels, as well as regulators of these channels. Loss-of-function mutations in the SCN5A gene, which codes for the cardiac sodium channel, are found in 11–28% of Brugada syndrome patients, but they are most common (about 62%) in the younger patients diagnosed (SCN5A has 300 mutations, the majority of which are found in the transmembrane-spanning regions) Such structural alterations are thought to have a role in Brugada syndrome by causing slower conduction. Other research has linked Brugada syndrome to structural and functional abnormalities.[2]

Clinical manifestation
Brugada syndrome has a wide range of clinical symptoms; some patients with the illness are asymptomatic while others die suddenly. When symptoms appear, they usually do so in the fourth decade of life. Palpitations, syncope, convulsions, and nocturnal agonal breathing have all been described as initial presenting symptoms. Intriguingly, up to 23% of patients who presented with cardiac arrest had a history of past syncope. Most patients are asymptomatic, however arrhythmic problems such as polymorphic ventricular tachycardia (VT) or ventricular fibrillation cause syncopal episodes or cardiac arrest in 17 to 42 percent of identified patients. As asymptomatic people go undiagnosed, this may represent an exaggeration of the true frequency. Supraventricular tachycardias have been found in up to 20% of Brugada syndrome patients. The prevalence of spontaneous atrial fibrillation (AF) is considerable (39%) and there is a higher risk of AF after

electrical stimulation. However, it is unknown if higher susceptibility to VAs is linked to atrial vulnerability. When there is a preponderance of vagal activity, such as during rest or sleep, arrhythmias and hence symptoms in Brugada syndrome emerge. These symptoms have a significant circadian peak (midnight to early morning), as well as a significant seasonal peak (spring to early summer).[3]

Diagnostic procedures

Three repolarization patterns were initially described:

a) Type-1 ECG pattern, in which a coved ST-segment elevation of less than 2 mm is followed by a negative T-wave with little or no isoelectric separation, with this feature present in more than one right precordial lead (V1 to V3)
b) Type-2 ECG pattern, in which an ST-segment elevation is followed by a positive or biphasic T-wave, resulting in a saddle-back configuration
c) ECG pattern Type-3, with a right precordial ST-segment elevation of 1 mm and either a coved or saddle-back morphology.

Types 2 and 3 aren't thought to be diagnostic. A provocative drug challenge test utilising intravenous Class 1A or 1C antiarrhythmic medications can cause the ECG type 1 pattern to appear spontaneously or be produced via a provocative drug challenge test. Flecainide, ajmaline, procainamide, disopyramide, propafenone, and pilsicainide have all been used to unmask BrS, although ajmaline and flecainide are currently the preferred medications. Clinical and electrocardiographic characteristics are used to diagnose BrS. As a result, when a patient meets at least one of the following criteria, BrS is certain to be diagnosed.

A. Family history: SCD in a 45-year-old relative or ECG type 1 in relatives
B. Symptoms of an arrhythmia, such as syncope, convulsions, or nocturnal agonal respiration
C. Ventricular arrhythmias[1]

Genetics of brugada syndrome

Brugada syndrome is passed down through the family in an autosomal dominant pattern. The gene encoding the -subunit of the cardiac sodium channel gene, SCN5A, was the first to be connected to the Brugada syndrome. SCN5A mutations restrict sodium ion access, disrupt the ion balance of the action potential, and cause ventricular tachycardia and ventricular fibrillation, which are cardiac rhythm abnormalities. SNC5A mutations have been found in about a quarter of patients, implying that the disorder could be caused by mutations in other genes.[4] Brugada syndrome is caused by mutations in the SCN5A gene, which account for 18–30% of cases. SCN5A mutations have been found to be more common in familial cases than in sporadic cases. Because the promoter region, cryptic splicing mutations, and the existence of large rearrangements are not routinely investigated, negative SCN5A results may not always rule out causal gene alterations.[5]

Dugs that cause brugada

Tricyclic antidepressants, lithium, diphenhydramine, alcohol, and cocaine have all been linked to the Brugada pattern. Isolated examples of beta blockers and calcium channel blockers inducing Brugada ECG patterns have been documented, and it's possible that this is related to blockage of L type calcium channels, which causes the epicardial action potential dome to shorten. ST elevation has also been linked to alpha agonists, insulin, and glucose. Vaughan Williams Class I drugs are probably the most effective in unmasking the Brugada ECG pattern. Flucainide, ajmaline, and procainamide are all members of this family and can be utilised in diagnostic testing to identify at-risk patients with inducible type I pattern ECG.[6]

Hypothesis of brugada syndrome

- **Repolarisation (Channelopathy) hypothesis:**

According to this theory, rebalancing currents at the end of phase 1 of the AP causes the AP notch in the RV's epicardium to become more prominent. The typical ST-segment elevation was thought to be caused by this accentuation. The epicardium and endocardium have non-homogeneous expression of the transient outward potassium current under normal conditions, with the epicardium having a higher expression of It0. Outward currents outweigh inward currents in the presence of pathological circumstances, such as a SCN5A mutation (leading to sodium channel loss-of-function), and the epicardium may undergo all-or-none repolarization. The loss of the AP dome at some epicardial locations, but not all, could result in significant epicardial repolarization dispersion (EDR). This causes a transmural voltage gradient, which causes a transmural dispersion of repolarization (TDR) between the epicardium and endocardium, resulting in the ECG's characteristic ST-segment elevation. Furthermore, when epicardial repolarization occurs before that of the myocardial and endocardial regions, the T-wave remains positive, resulting in the type-2 or saddleback ECG. When the AP is prolonged in the epicardial area, repolarisation across the RV wall is reversed, resulting in an inverted T-wave and a type-3 coved-type ECG. At regions of early repolarisation, the conduction of an AP dome causes local re-excitation via a phase 2 re-entry mechanism, which favours the formation of additional systolic beats.

- **Depolarisation (Conduction Delay and Mild structural defects) hypothesis:**

The RV membrane potential is more positive than the RVOT during the first portion of the cardiac cycle, directing the intercellular current to the RVOT. The current then returns from the RVOT to the RV via the extracellular space. During this time, an ECG electrode placed above the RVOT records a positive signal, resulting in the Brugada ECG's ST-elevation. As a result, the membrane potentials in the RVOT are higher than in the RV, and the potential gradient is reversed. A negative T-wave is produced when the RVOT drives the current in the opposite direction, away from the RVOT

electrode. Further research suggests that the type-1 ECG is characterised by a conduction delay. Premature beats originating in the border zone between delayed and early depolarisation, similar to what occurs in the context of regional transmural ischaemia, are hypothesised to generate the re-entry circuit that leads to a VA. There is some indication that modest structural abnormalities, which were previously undetectable by conventional cardiac imaging, are involved. Focal fibrosis, myocarditis, apoptosis, and fibrofatty replacement of the RV free wall with RV enlargement, dilatation, and RVOT enlargement are among the structural abnormalities identified in Brugada patients.[2]

Phenotype modulators

Recently, genetic and environmental modulators that play a key role in the dynamic character of the ECG and may also be responsible for ST segment elevation have been found. When genetically predisposed patients are exposed to these conditions, they may develop a poorer phenotype; consequently, preventive actions must be taken. By lowering calcium currents, bradycardia and vagal tone may contribute to ST segment elevation and fatal arrhythmia. This explains why ST segment elevation is higher in vagal circumstances and ventricular arrhythmias are more common at night.. Temperature is the most well-known environmental element that influences the BrS phenotype. The Nav 1.5 sodium channel's premature inactivation has been demonstrated to be exacerbated at higher temperatures. Drug-induced BrS, such as cocaine overdose, has also been observed. Cocaine is a sodium channel blocker that causes myocardial depression, life-threatening ventricular arrhythmias, and sudden cardiac death. Several drugs, including antidepressants, antiarrhythmics, and anaesthetics, have been linked to an increased risk of ST elevation and even arrhythmias in people who are genetically predisposed.[2]

Mutations causing a loss of function of calcium channel current

Many cases of BrS have been linked to mutations in the CACNA1C gene, which codes for the -subunit of the human L-type voltage-gated calcium channel, CaV1.2.

The gene CACNB2B encodes the -subunit of CaV1.2, Cav2, which is implicated in ICaL regulation and intracellular trafficking. BrS has been linked to a number of loss-of-function mutations in the ICaL gene.

CACNA2D1 encodes the voltage-dependent calcium channel's 2 subunit and shares functional characteristics with Cav2. SQTS, IVF, ERS, and BrS have all been linked to loss of function mutations in this gene.

Mutations causing a gain of function of potassium channel currents

KCNE3: KCNE3 (MiRP2) gain of function mutations have been linked to BrS. The control of various cardiac potassium currents, including Ito and IKs, is MiRP2's primary function. When KCNE3 mutations are co-expressed with WT-KCND3, it results in a gain-of-function and faster Ito kinetics.

KCND3—A gain-of-function mutation in KCND3 has similarly been linked to BrS and has been demonstrated to raise Ito. Kv4.3, the Ito channel's -subunit, is encoded by KCND3.

SCN1B— When co-expressed with WT-KCND3, BrS-related mutations in the SCN1B gene, which encodes the auxiliary NaV1 subunit of the voltage-gated cardiac sodium channel, can reduce INa while significantly increasing Ito.

Mutations in KCNJ8, which encodes Kir61, have been shown to cause gain-of-function in IK-ATP, a channel that is normally closed under normoxic conditions. Due to the abbreviation of action potential length, this causes an accentuation of the action potential notch as well as a depression of the plateau, resulting in the BrS phenotypic or SQTS phenotype.[7]

Abnormal conduction in rvot in brugada syndrome

In Brugada syndrome patients, structural anomalies produced by interstitial fibrosis are critical in the development of ST segment elevation and the initiation of arrhythmias. These structural changes result in a branching and converging cardiac network that closely resembles the network of surviving fibres in infarcted myocardium. When the depolarizing current generated by the proximal myocardial is insufficient to activate the distal myocardium (current-to-load mismatch), this might induce activation delay at the branching point and potentially excitation failure. The safety factor for cardiac conduction, also known as conduction reserve, is the ratio of the current generated to the minimum current required to maintain propagation. Conduction safety is reduced by sodium channel blockade, which enhances conduction block at branching locations. The provocation test is based on this impact of sodium channel blocking, which explains the greater occurrence of mutations in the gene (SCN5A) encoding the cardiac sodium channel in the Brugada syndrome population.[8]

Overlapping syndromes

BrS, early repolarization syndrome (ERS), progressive cardiac conduction disorder (PCCD), and other conditions that cause ventricular arrhythmias and syncope/SCD are among the overlapping syndromes.

- Early repolarization syndrome: J-point elevation, ST segment elevation with upper concavity, and significant T waves in at least two contiguous leads are all signs of early repolarization syndrome (ERS). The ECG tracings of ERS and BrS are comparable, however the extent to which they overlap is unknown. 84 ERS has been linked to several loss-of-function pathogenic variants in the CACNA1C, CACNB2, and CACNA2D1 genes, as well as gain-of-function pathogenic variants in the KCNJ8 gene. In patients with ERS, a pathogenic variation in the SCN5A gene has recently been discovered.
- Progressive cardiac conduction disease: PCCD, also known as Lev-Lenègre syndrome, is a rare condition

in which the cardiac conduction system is disrupted due to degeneration of the His-Purkinje system. This condition is linked to syncope and even SCD. Because both diseases are caused by a decrease in INa, and PCCD has been described as a distinct expression of the BrS hereditary trait, the prevalence of PCCD in BrS families is not uncommon.

- Sick sinus syndrome: Sick sinus syndrome (SSS) is characterised by chronic sinus bradycardia, sinus arrest, atrial standstill, and tachycardia–bradycardia syndrome, all of which are linked to sinoatrial node dysfunction. Patients have reported a wide range of symptoms, including syncope and even SCD. Depending on the severity of the underlying heart condition, SSS might be intermittent and unpredictable. SSS has been linked to numerous pathogenic mutations in SCN5A so far. Furthermore, BrS and SSS were both found to be caused by a loss-of-function trait in INa within a single family.
- Long QT syndrome type III: Long QT syndrome (LQTS) is an inherited arrhythmogenic condition characterised by a prolonged QT interval, which can lead to ventricular tachyarrhythmias, syncope, and potentially sudden cardiac death (SCD). In contrast to pathogenic mutations linked with BrS, SCN5A pathogenic variants associated with LQTS cause gain-of-function (inducing loss-of-function). It's still unclear how a pathogenic variant in the same gene can cause nearly opposite electrical abnormalities. The biophysical features of the altered channel, co-inherited genetic variants, gender, ethnicity, or even other environmental factors may all influence the electrical malfunction.
- Atrial fibrillation: In clinical practise, atrial fibrillation (AF) is the most common arrhythmia. It's marked by a chaotic electrical activity in the atria, which results in irregular ventricular rates. There are no P waves on the ECG, and the R–R intervals are uneven. Despite the fact that the reaction to AF is so variable, it requires pharmacological treatment. AF with signs of PCCD and extended atrioventricular and atrial His conduction is seen in approximately 30% of BrS patients having a pathogenic mutation in the SCN5A gene.[2]

Pathophysiology

One of the "channelopathies" is Brugada syndrome. Changes in the transmembrane ion channels responsible for the cell action potential cause these circumstances, which enhance arrhythmia susceptibility. Although sporadic occurrences are known to occur, autosomal dominant transmission is the most common. In about 20 to 25 percent of people, mutations in the SCN5A gene, which codes for the alpha subunit of the heart sodium channel, have been found. Numerous mutations have been found, with the majority resulting in a decrease of sodium channel current. The low frequency of SCN5A mutations in affected patients, however, suggests genetic variability. The syndrome may be caused by an imbalance between the inflow and outflow currents during the cardiac action potential, according to recent studies of calcium channel anomalies in such patients. the cellular and molecular underpinnings of diagnostic ECG abnormalities, as well as the risk of ventricular fibrillation and sudden death Loss of sodium channel function causes current imbalances during phase 1 of the ventricular action potential, as well as a distinctive notch in epicardium but not endocardium. The ST segment elevation is caused by the ensuing transmural voltage gradient. Because right ventricular epicardial and mid-myocardial cells have more prominent transient outward currents than left ventricular epicardial and mid-myocardial cells, the right ventricular outflow system is more vulnerable to these ECG alterations. The vulnerability to ventricular arrhythmias is explained by a current imbalance that creates a vulnerable window during which an extrasystole might cause a phase 2 re-entry arrhythmia. This misalignment of inward and outward currents also explains some of the syndrome's characteristics, as well as the effects of various modulating medications and situations that have been utilized to confirm diagnosis and design treatment.[9]

Risk Stratification and Treatment

Syncope and abrupt death are common symptoms of Brugada syndrome. Heart arrhythmias are most common during rest or sleep, but they can also be provoked by fever, large meals, or excessive alcohol consumption. The insertion of a cardioverter-defibrillator is the only effective treatment for sudden death prevention. The difficulty for clinicians is to identify individuals who are likely to benefit from the preventive implantation of a defibrillator. One of the goals of Brugada syndrome research has been to use risk stratification to identify people who are at danger of sudden death. Patients with a history of syncope and a spontaneous abnormal ECG are at the highest risk, according to studies. In these patients, implanting a cardioverter-defibrillator has proven to be an effective primary preventive strategy. The utility of numerous non-invasive markers for risk classification in Brugada syndrome has been evaluated. The majority of these variables were shown to have insufficient positive predictive value for determining who would benefit from the implantation of a cardioverter-defibrillator.[4]

Treatment options for brugada syndrome:

1. **Device therapy:**
   - Implantable cardioverter defibrillator (ICD)—ICD implantation is first-line therapy for patients who have had their SCD aborted or who have documented VT/VF with or without syncope.
   - Pacemaker therapy—Despite the fact that life-threatening arrhythmias are most commonly linked with slow heart rates and occur during sleep or at rest, a potential therapeutic role for cardiac pacing has been completely unexplored204 and is restricted to a few case studies. Electrical storms that cause many acceptable ICD discharges in BrS patients indicate the necessity for supplementary therapy.

Heart transplantation was the sole option for these patients before the development of ablation methods.[7]

2. Intraoperative care

External defibrillator pads should be placed on all patients, even those without an ICD, prior to induction of anaesthesia. Tachyarrhythmia can be exacerbated by alterations in the autonomic nervous system. Inadequate analgesia, mild anaesthesia, and postural shifts are all known to alter autonomic tone and should be avoided. Bradycardia or increased vagal tone as a result of surgical stimulation have also been linked in the development of Brugada ECG abnormalities, therefore the depth of anaesthesia should be balanced to minimise these effects. Because of the danger of bradycardia, some people recommend avoiding suxamethonium and instead utilising prophylactic glycopyrrolate before intubation. Temperature fluctuations, particularly rises, can reveal the condition. To sustain normothermia, the patient should be warmed or cooled as needed, with monitoring in all except the most extreme situations. Procainamide and flecainide, which inhibit sodium channels, are contraindicated. Beta-adrenergic blockade and alpha-receptor stimulation (norepinephrine and methoxamine) can exacerbate Brugada syndrome symptoms, whereas beta-adrenergic stimulation reduces them.

3. Postoperative care

Before removing external defibrillator pads, any patient with an ICD should have it turned back on as soon as feasible. Arrhythmias can occur after surgery, hence doctors prescribe a period of continuous ECG monitoring with ST analysis for up to 36 hours. During this period, all modifying elements should be kept in mind. Alternative antiemetic medication should be used because phenothiazines are generally contraindicated.[10]

Pharmacological therapy

Quinidine, a non-specific inhibitor of cardiac transient outward current (Ito), has been recommended as a BrS gene-specific treatment. This hypothesis is based on the assumption that the loss of sodium inward current in BrS causes an anomalous shift in the outward direction near the conclusion of phase 1 of the action potential, tilting the balance between outward and inward currents. This situation causes repolarization dispersion and an arrhythmogenic substrate because the transmural distribution of transient inward current is not uniform. Quinidine could restore equilibrium by blocking repolarizing currents, notably Ito, which is active during the first phases of the action potential. Some authors have proposed a gene-specific treatment approach for BrS based on this intriguing notion.[11]

CONCLUSION

BrS is a serious inherited cardiac illness that causes ventricular arrhythmias and heart failure. Variable expressivity and partial penetrance are caused by mechanistic processes that are still unknown. The need to improve stratification accuracy and therapy where the occurrence of complications is a strong limiting factor stems from the identification of intermediate-risk patients. The next step toward customised therapy could be a mix of risk variables in an integrated clinical and genetic score. The introduction of novel defibrillation technologies, such as a subcutaneous ICD, may make the decision easier by lowering the rate of ICD-related problems. Finally, catheter ablation, which is currently only available to the most severely symptomatic individuals, should be considered as a way to reduce arrhythmic risk. Long-term research are still needed before this approach may be used on asymptomatic patients.

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