Brugada syndrome. Physiopathological, clinical aspects and their association with infectious diseases

Juan Sebastián Rodríguez-Constatín¹, Nelson Adolfo López-Garzon², Carlos Alberto Navia-Amezquita³, Diana Lorena Mora-Obando⁴, Rosa Amalia Dueñas-Cuellar⁵

¹ Student, Medicine Program, Faculty of Health Sciences, University of Cauca, Colombia.
² Teacher, Department of Internal Medicine, Faculty of Health Sciences, University of Cauca, Colombia.
³ Teacher, Department of Physiological Sciences, Faculty of Health Sciences, University of Cauca, Colombia.
⁴ PhD student, Evolutionary and Translational Venomics Laboratory, Biomedicine Institute of Valencia, Spain.
⁵ Teacher, Department of Pathology, Faculty of Health Sciences, University of Cauca, Colombia.

Corresponding author: Rosa Amalia Dueñas-Cuellar; raduenasc@unicauca.edu.co

Received: May 21, 2018
Accepted: September 11, 2018

This manuscript was approved for publication by the Iatreia Magazine taking into account the concepts given by the peer reviewers. This is a preliminary edition, whose final version may present changes.

**SUMMARY**

Brugada syndrome (BrS) is a non-structural cardiac disease that affects cardiac ion channels; it is characterized by clinical manifestations such as arrhythmias, tachycardia, syncope and sudden death, among others. Its diagnosis is mainly electrocardiographic, with a highly suggestive but not pathognomonic pattern, thus, there could be differential diagnoses from the electrocardiographic point of view.

There are three electrocardiographic patterns in patients with BrS, of which type I is the most characteristic pattern. Currently, multiple genes have been linked to the presentation of this syndrome, among which the SCN5A gene is the most described in the literature. It is known that this syndrome is more frequent in males; however, there are not epidemiological studies in Latin America to confirm it. Although research around the causal mechanisms of the syndrome has advanced, there are several unresolved issues, for example, its masking by the signs produced for some infectious diseases caused mainly by viruses. Therefore, given the clinical relevance of the topic, for the medical general practitioner and the specialist, the objective of this review is to describe not only the physiopathological and clinical aspects of the disease, but also to highlight cases of patients with infectious diseases, who subsequently have been diagnosed with Brugada syndrome.
INTRODUCTION

Brugada Syndrome (BrS) was first described in 1992 by Pedro and Josep Brugada (1). It is a non-structural heart disease, causing 4 to 12% of all sudden deaths in people who usually do not experience any symptoms; between 20 and 50% of these deaths occur in patients with no demonstrable structural heart disease, and as a consequence of an arrhythmia (2-4).

The genetic bases of the disease have shown that it has autosomal dominant origin and that approximately 20 genes associated with more than 250 mutations have been isolated (5, 6). However, there are de novo diagnoses in which the disease screening in direct relatives has no history (7). The main symptoms include: tachycardia, syncope, arrhythmias and sudden death as a final outcome (8).

Some research suggests that asymptomatic patients have an increased risk of sudden death due to the lack of a timely diagnosis (9), another research reports that the presence of symptoms is a risk factor for the syndrome (10, 11) and another, that the evolution is similar in both, symptomatic and asymptomatic patients (12). Therefore, anyone with electrocardiographic patterns (ECG) characteristic of the syndrome, should be classified as a high-risk patient (13). Nevertheless, it should be noted that the electrophysiological study is highly questioned as a risk stratification method in Brugada syndrome (14, 15).

Three electrocardiographic patterns have been described in BrS, of which type I is the characteristic pattern of the syndrome (16). Although these patterns are the basis for the
diagnosis of BrS, some patients show a hidden or intermittent form, which requires other methods for their diagnosis (17).

It is estimated that the prevalence of BrS is 1 per 2,000 individuals in the World. However, there are differences in these figures depending on the geographical location (18); For example, in Western countries such as Spain, Italy, Belgium, the Netherlands, Greece, Germany, Austria, Switzerland, Poland, Ukraine and France, the approximate prevalence is from 1 to 5 cases per 10,000 inhabitants (19, 20), while in Eastern countries, 1 in every 2,500 people has the syndrome (21). Some of these cases have been reported in cities such as Japan, Thailand, China, India, Laos, Vietnam, Singapore, and Cambodia (22).

In the American Continent there have been no epidemiological studies on the subject, so the exact number of cases is unknown; despite this, some cases have been reported in countries such as the United States, Canada, Brazil, Argentina and Uruguay (23-27). In Colombia, there have been cases reported in Bogotá (28), Cali (29) and Medellin (18), however, the number of cases for the country could be underestimated. In the city of Popayan, for example, although there are clinical observations that suggest its presence, the cases have not been published.

Factors such as gender can influence the clinical presentation of the disease (30, 31). Epidemiological studies suggest that there is a higher prevalence in males than in females in a ratio of 8:1 (32), probably due to the regulating action of sex hormones, which allow a greater expression of genes sensitive to steroid hormones, particularly in testosterone (33), which favors a greater expression of sodium channels at the cardiac level (34, 35).

In this sense, it has been found that in some patients with Brugada syndrome, high levels of testosterone are associated with the presence of the characteristic phenotype of BrS
and explain the predominance of the syndrome in males (36). In addition, these patients are characterized by a lower percentage of visceral fat, secondary to this hormonal influx due to higher levels of testosterone (37, 38).

Men with Brugada syndrome have a higher risk clinical profile than women and have a worse prognosis (39, 40). Other studies have described that the type I ECG pattern, which is characteristic of the disease, occurs less frequently in women (41). In spite of the above, there is limited and not entirely clear information on the differences regarding gender in BrS (42).

Electrocardiographic patterns characteristic of BrS have been found in patients with some type of infection, whether viral, parasitic or bacterial, as a result of the rise in the normal temperature, increase that can accelerate the inactivation of the sodium channels, reproducing the type I electrocardiographic phenomenon (43). Multiple cases of patients have been reported in the literature in which, due to symptoms such as fever caused by infectious diseases, it is possible to unmask a hidden BrS (44-48).

**PHYSIOPATHOLOGY AND PATHOGENESIS OF BRUGADA SYNDROME**

The heart is a muscular organ whose main function is to provide blood to all human body tissues. Electrophysiologically, it has an action potential of approximately -85 mvol at rest, and achieves a membrane potential of approximately 20 mvol (depolarization) in each beat. Cardiac depolarization has been divided into 5 phases (0 - 4), each of which is determined by the entry and exit of $K^+$, $Na^+$, $Ca^{+2}$ ions (Figure 1. A) (49). Phase 0 is characterized by the entry of $Na^+$ into the intracellular space through voltage-dependent channels, and at the same time the opening of slow channels of $Ca^{+2}$ occurs, this causes the cardiac cell to depolarize and its membrane potential to increase until reaching the
spike or tip (20 mvol), at such time all the Na$^+$ channels close. After inactivation of the Na$^+$ channels, K$^+$ exit and Cl$^-$ entry occur, which defines phase 1 of the myocardial potential. During this transient phase, a rapid repolarization occurs in which the membrane potential returns to 0 mvol. Phase 2, also known as cardiac plateau phase, takes between 0.2 and 0.3 seconds, and results in the entry of Ca$^{2+}$ and Cl$^-$. During phase 3 the slow channels of Na$^+$ and Ca$^{2+}$ close and the exit of K$^+$ increases, as a result, a rapid repolarization takes place, which takes the cell back to its negative potential (-85 mvol). Finally, phase 4 occurs, which allows the chemical equilibrium of the ions at the intra and extra cellular levels, this electrolytic restitution is achieved by the action of the Na-K-ATPase pump, which expels the excess of Na$^+$ that is found at intracellular level and K$^+$ enters by active transport, conserving the negative potential of the cell; in the same way, the Na$^+$/Ca$^{2+}$ exchanger allows the exit of a Ca$^{2+}$ ion by the entry of 3 Na$^+$ ions (Figure 1. A and D) (50-52).
Figure 1. Action potentials associated with the electrocardiographic patterns of Brugada syndrome

A. Normal cardiac action potential. B. Action potential associated with the type I pattern. C. Action potential associated with the type II pattern. D. Normal channels action during action potential. E. Sodium channel blockade originating the electrocardiographic patterns of Brugada syndrome. Source: adapted from Brugada et al. (2009).

In the BrS, the normal action potential shows alterations and so far two hypotheses have been described to explain its involvement in pathogenesis. The first one, known as repolarization deterioration, explains that the imbalance of positive charges by ion currents alteration of phase 1 potential leads to a loss of the plateau, shortening it by 40 to 70% in the epicardium (Figure 1 B) (53, 54). This can be triggered as a result of the Ca\(^{2+}\) or Na\(^{+}\) inflow currents decrease or, by an increase in the K\(^{+}\) transient outflow currents between the right epicardium and the endocardium, which causes a transmural dispersion of the repolarization and refractoriness, giving rise to the typical ECG pattern (type I), where is presented the ST elevation (21, 55) observed in right precordial leads (56).
The second hypothesis is called depolarization theory; this is secondary to a conduction delay in the anterior epicardial region of the right ventricular outflow tract. This is explained by the existence of some areas with abnormal potentials, with low voltage and prolonged duration, something that does not happen at the level of the anterior endocardium of the same outflow tract, nor in other areas of the right and left ventricles (Figure 1. C) (57). The arrhythmias and sudden death that characterize BrS are due to the development of a reentry mechanism in phase 2, as a result of the heterogeneity and dispersion of repolarization, both at the transmural and epicardial level, with a greater vulnerability in the premature ventricular complexes occurrence (58). The heart has a normal electrical activity known as the cardiac cycle, in which all the cells of the heart are depolarized sending them to a refractory state and thus avoiding a new excitation; however, if a group of fibers are not timely activated in the cycle, either by delay or early activation, they can activate previously depolarized zones that were recovered from the initial activation, so a second potential is generated, which will produce a phenomenon of reentry and will re-depolarize certain heart cells that have already been repolarized by the first potential (59). All these phenomena can be demonstrated with the administration of Flecainide (60, 61), an antiarrhythmic drug that, along with ajmaline, are sodium channel blockers and, therefore, are essential drugs for the diagnosis of BrS (62). The test is considered positive if during drug perfusion in the patient, the ECG, whether type II or III, becomes type I ECG diagnosis, characterized by a rise of the ST segment ≥ 2 mm followed by negative T in more than a right precordial derivation (V1-V3) (63, 64). Factors external to the heart can also influence the appearance of arrhythmias, for example the autonomic tone (65). Some authors describe a sudden increase in vagal activity immediately before the onset of ventricular fibrillation, which may confirm that an arrhythmia can occur in several ways. The existence of a loss of balance between the
sympathetic and the parasympathetic tones in the BrS has been reported. The risk of arrhythmias increases when a reduction in the sympathetic activity occurs with a predominance of the parasympathetic tone, this could be the reason why the incidence of arrhythmias and sudden death occur at rest or during sleep (where there is an increase in the parasympathetic tone), it should be noted that this phenomenon occurs in subjects with BrS and not in other pathological circumstances in which, on the contrary, the increase in sympathetic tone is the arrhythmia generator (66, 67).

**GENETIC BASES**

The BrS has an autosomal dominant pattern of transmission with incomplete penetrance (68). It is known that 25% of patients have some mutation in the gene (3p21) (5). This encodes the α subunit of the sodium channel Nav1.5, which determines phase 0 of the cardiac action potential (69). Mutations in this gene generate the loss of sodium channel function by reducing the incoming ion current, which causes the clinical manifestations and the ECG pattern characteristic of BrS (70). The α subunit of this sodium channel in turn interacts with the β1 subunit, ankyrin G, caveolin 3 and syntrophin; therefore, mutations in the genes that code for these proteins have also been associated with the syndrome (71).

Other mutations related to BrS have been found (72), for example the mutation in the SCN10A gene, which codes for the sodium channel Nav1.8, leads to a loss of its function, and decreases the Na\(^+\) current by modulation of the activity of the Nav1.5 channel encoded by SCN5A, alterations that prolong the PRI and QRS intervals (73, 74). Another mutation related to BrS is the one that occurs in the gene similar to glycerol-3-phosphate dehydrogenase-1 (GPD1L), which acts as a modulator of ion channels, although the exact
mechanism is unknown (75). On the other hand, the mutation in the SCN1B42 gene prevents the opening of the Na\(^+\) channel and mutations in the SCN3B43 gene cause reduction of the Na\(^+\) current by interference in the normal traffic of the channel towards the cell membrane (59). Recently, it has been shown that dominant negative mutations in the RANGRF gene, which codes for the MOG1 protein, impair the regulation of sodium channel expression and traffic to the membrane, leading to the reduction of sodium currents, and therefore to the manifestations of the syndrome (76).

Mutations have also been isolated in the genes encoding the \(\alpha-1\) (CACNA1C), \(\beta\)- (CACNB2b) and \(\delta1\) (CACNA2D1) subunits of the cardiac Ca\(^{2+}\) type L channel, causing a decrease in the Ca\(^{2+}\) input current. This condition is related to 10-15% of cases of BrS and short QT syndrome (77-80). Mutations in the KCNE347 and KCNE5 genes cause the increase of transient K\(^+\) outflow. Finally, mutations in KCNJ8 block the potassium channel, preventing the exit of the ion, and resulting in the loss of the cardiac plateau (81, 82).

**CLINICAL MANIFESTATIONS AND DIAGNOSIS**

Patients with BrS have no obvious signs of structural heart disease, but they have malignant ventricular arrhythmias, syncope, or sudden cardiac death, which usually occur at rest or during nighttime sleep (83). In addition, they may present polymorphic ventricular tachycardia (PVT) episodes which end in ventricular fibrillation (VF). The occurrence of three or more episodes of ventricular tachycardia or separate ventricular fibrillation requiring therapy with implantable automatic defibrillator (ICD) in a period of 24 h is known as an electrical storm, a rare but potentially fatal phenomenon (84- 86). These ventricular arrhythmic events are observed more frequently in the fourth decade of
life, although cases have been described between 19 and 56 years (48, 87-89), as well as in the pediatric population (90).

The clinical manifestations of the syndrome include a history of syncope, nocturnal agonal breathing while sleeping, a family history of sudden death before the age of 45, documented ventricular fibrillation, polymorphic ventricular tachycardia, and the presence of the type I electrocardiographic pattern in a family member (82); these manifestations are useful for directing the therapeutic intervention of the patient.

Currently, the diagnosis of BrS is based on electrocardiographic criteria. According to the current consensus on the diagnosis and management of patients with inherited primary arrhythmia syndromes from the Heart Rhythm Society and the European Heart Rhythm Association, three different ECG patterns have been described for BrS, which are characterized by the presence of a morphology similar to a right bundle branch block, except that there is an elevation of the ST segment in the right ventricular precordial leads (V1, V2), with the electrodes located in the 2nd, 3rd or 4th intercostal space (91, 92).

The type I pattern is characterized by a convex and descending elevation of the ST segment ≥ 2 mm in more than one right precordial lead (V1-V2), with negative T waves, elevation that occurs spontaneously or after administering class I antiarrhythmic drugs intravenously. The type II pattern is characterized by ST segment elevation ≥2 mm in right precordial leads followed by positive or isobiphasic T waves (saddle-shaped ECG) and, the type III pattern is defined as either of the two previous patterns, but with elevation of the ST segment ≤ 1 mm (Figure 2) (21, 93-95) and, since this pattern shows a non-significant ST elevation, it is not completely suggestive of this channelopathy (7).
Figure 2. Electrocardiographic patterns of Brugada syndrome.

A. Type I electrocardiographic pattern, the arrow shows the convex and descending elevation of the ST segment $\geq 2$ mm negative T waves. B. Type II electrocardiographic pattern, ST segment elevation $\geq 2$ mm T positive or isobiphasic, saddle-shaped waves (indicated by an arrow). C. Type III electrocardiographic pattern, the arrow indicates the ST segment elevation is $\leq 1$ mm. Source: adapted from Brugada et al. (2009).

The last two patterns are diagnosed by pharmacological test with class 1 antiarrhythmic drugs which induce the morphology of a type I ECG (62, 63). To confirm the BrS, an ECG should be performed and it should be evaluated if this corresponds to the type I electrocardiographic pattern, characteristic of the syndrome. It is suggested that every patient with asymptomatic type I pattern should undergo a thorough interview, a physical examination, and a register of a conventional ECG with modified derivations; it is also recommended to study all consanguineous relatives (96). If type II or III patterns are presented, confirmation of the diagnosis is required by performing the ajmaline, procainamide, or flecainide test (97).
It is important to highlight that some diseases can present electrocardiographic records similar to the BrS, for example acute myocardial infarction, acute myocarditis, right ventricular infarction, acute pulmonary thromboembolism, hyperkalemia, arrhythmogenic dysplasia of the right ventricle, right and left branch block, left ventricular hypertrophy, and dissecting aneurysm of the aorta, which makes differential diagnosis difficult (98).

Some conditions, such as febrile episodes, may unmask silent forms of BrS and/or confer an increased (transient) risk of ventricular arrhythmias (99), especially in the pediatric population (100), where the identification of BrS is unusual and the majority of reported cases are unmasked after febrile episodes (101).

**UNMASKING BRUGADA SYNDROME THROUGH INFECTIOUS DISEASES**

Several cases of BrS electrocardiographic patterns have been reported in patients with some type of infection, whether viral, parasitic or bacterial infection. These infections elevate the normal temperature until reaching fever (morning temperature > 37.2 °C or an evening temperature > 37.7 °C) (46, 102). This rise in temperature can accelerate the inactivation of the sodium channels with a slower recovery, and cause the appearance of the supra-leveling of the ST segment in the right precordial leads (43).

Below, some cases of patients with infectious diseases who were diagnosed with the syndrome after suffering episodes of fever during the clinical pictures of the disease are described. The case of a 51-year-old female patient from Badajoz, Spain has been reported, with a personal history of type II mellitus diabetes, smoker of 3 cigarettes a day and with arthrosis, admitted with fever and abdominal pain with 24 hours of evolution, located in the left iliac fossa, accompanied by nausea and food vomiting. In the physical
examination it is highlighted that the fist percussion was positive, in the electrocardiogram it presents a Brugada type II pattern during the febrile episodes of an acute pyelonephritis due to Enterobacter aerogenes isolated in blood cultures and urinalysis, it should be noted that the ECG normalizes in the afebrile periods (103).

In viral infections, where a febrile syndrome develops, an ST-segment elevation may occur with the appearance of some BrS ECG pattern, the most common in these cases being the type I pattern, where the decrease in fever makes the pattern disappear (104). The following cases describe the previous situation, the first one is a 49-year-old man, who was admitted for investigation of recurrent syncope, episodes that had begun after the H1N1 virus infection (2009 Pandemic) and which appeared again during pneumonia febrile symptoms after influenza. A 12-lead electrocardiogram (ECG) (Figure 1), recorded while the patient was febrile (temperature 38.3 °C), showed an ST segment elevation in leads V1-V3, consistent with a type I pattern. Time after the fever resolved, the electrocardiographic pattern disappeared (105). The second one is the case of a 58-year-old man who presented at the hospital with throat ulcer, cough and 38.5 °C fever; the ECG showed an elevation of the ST segment in leads V1 to V3 compared to the initial electrocardiogram, while the cardiac enzymes, the chest radiography, the two-dimensional echocardiography and the coronary arteriography were normal. All these symptoms were attributed to a viral disease; the ST-segment elevation was resolved with the decrease in fever (106). Additionally, some cases of type I pattern in patients with malaria, and the disappearance of the pathological ECG at the time of the patient's improvement are reported (107, 108).

When taking into account the above, it is important to consider BrS as a differential diagnosis in patients who are in a feverish state, who have precordial pain or other features of infarction, accompanied by electrocardiographic findings suggestive of Brugada
syndrome (109), since type II pattern cases on the electrocardiogram due to pericarditis have also been reported. For example, in a 27-year-old man from Perugia, Italy, who went to the doctor because of fatigue and discomfort in his chest; the laboratory findings showed an increase in the white blood cell count and the C-reactive protein. The patient was admitted with a diagnosis of pericarditis, however, the electrocardiogram showed an elevation of the ST segment of the "saddle-shaped" type in lead V2, recognized as a type II Brugada pattern. A few days after starting the anti-inflammatory therapy, the ECG normalized (110). It should be taken into account that presenting a BrS pattern when the temperature is high increases the risk of presenting arrhythmic events and suffering a fatal outcome due to sudden death (111).

TREATMENT

When this syndrome is suspected in a patient, it is recommended to avoid some risk factors that increase ST segment elevation, such as antiarrhythmic drugs (procainamide, propafenone) (112), psychotropic drugs (amitriptyline, lithium) and anesthetics/analgesics (procaine and propofol), among others (cocaine, alcohol) (113).

Currently, BrS is treated with certain drugs or with the use of an implantable cardioverter defibrillator (ICD) in symptomatic patients (Table 1); however, in asymptomatic patients it is very difficult to decide on a therapeutic behavior (114-116). The available drugs are quinidine, which has proved useful in the treatment of patients who develop electrical storms, as well as isoproterenol, disopyramide and orciprenaline (117-119).
Table 1. Recommendations for the use of the ICD during the treatment of a patient with Brugada syndrome according to the Declaration of consensus on the diagnosis and treatment of patients with hereditary primary arrhythmia syndromes

<table>
<thead>
<tr>
<th>Class I</th>
<th>The following lifestyle changes are recommended in all patients diagnosed with BrS.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Avoiding drugs that can induce or aggravate ST segment elevation in right precordial leads.</td>
</tr>
<tr>
<td></td>
<td>Avoiding excessive alcohol intake.</td>
</tr>
<tr>
<td></td>
<td>Treating fever immediately with antipyretic medications.</td>
</tr>
<tr>
<td></td>
<td>The ICD is recommended in patients with a diagnosis of BrS who:</td>
</tr>
<tr>
<td></td>
<td>are survivors of cardiac arrest and/or,</td>
</tr>
<tr>
<td></td>
<td>have a documented sustained spontaneous ventricular tachycardia (VT) with or without syncope.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Class IIa</th>
<th>The ICD implant may be useful in patients with a type I ECG of spontaneous diagnosis who have a syncope history, probably caused by ventricular arrhythmias.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Quinidine may be useful in patients with a diagnosis of BrS and history of arrhythmic storms defined as more than two VT/V episodes in 24 hours.</td>
</tr>
<tr>
<td></td>
<td>Quinidine may be useful in patients with a diagnosis of BrS when:</td>
</tr>
<tr>
<td></td>
<td>the patient qualifies for an ICD but has a contraindication to use it or refuses to do it and/or,</td>
</tr>
<tr>
<td></td>
<td>the patient has a history of documented supraventricular arrhythmias requiring treatment.</td>
</tr>
<tr>
<td></td>
<td>The isoproterenol infusion may be useful to suppress arrhythmic storms in patients with BrS.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Class IIb</th>
<th>ICD implantation can be considered in patients with a diagnosis of BrS who develop ventricular fibrillation (VF) during programmed electrical stimulation.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Quinidine can be considered in asymptomatic patients with a diagnosis of BrS with a type I spontaneous ECG.</td>
</tr>
<tr>
<td></td>
<td>Catheter ablation can be considered in patients with a diagnosis of BrS and history of arrhythmic storms or repeated discharges of the ICD.</td>
</tr>
</tbody>
</table>

| Class III | ICD implantation is not indicated in patients with asymptomatic BrS with a type I ECG induced by drugs, with a family history of only one sudden cardiac death. |

Source: adapted from Priori et al. (2013).

It is important to note that, according to the current consensus, only quinidine and isoproterol are recommended for the pharmacological management of the Brugada syndrome (120). Some anesthetic drugs manage to maintain normal heart rates in patients with BrS due to their properties on the autonomic nervous system, their administration is aimed at avoiding the cardiac sodium channel dysfunction and at preventing some complications such as arrhythmias (121). Nevertheless, pharmacological treatment for
BrS is not very effective (4). The implantation of an ICD prevents sudden death in symptomatic patients with type I ECG (122, 123); in addition, if unfavorable effects such as VT or VF malignant arrhythmic events occur, the ICD ends the previous situations with anti-tachycardia stimulation or with defibrillation therapy, thus avoiding cardiac arrest and subsequent sudden arrhythmic death (124).

For patients with Brugada syndrome who have survived a sudden cardiac arrest or those with a history of syncope, which is believed to be due to ventricular tachyarrhythmias, the implantation of an ICD is recommended instead of an antiarrhythmic drug treatment, such as it is shown in Figure 3.
CONCLUSIONS

Epidemiological studies on BrS have not been carried out in the American continent, so the exact number of cases is unknown. It is known that this syndrome is genetically heterogeneous, since the genetic causes are multiple when mutations occur in various genes that code for the sodium, potassium and calcium ion channels. For this reason, the usefulness of diagnostic tests based on a single genetic marker could be ambiguous.
It should be taken into account that multiple factors such as gender, age, family history, type and penetrance of mutation can influence the development of BrS and determine its symptomatology.

Some possible inducers of BrS electrocardiographic patterns have been described, for example, febrile episodes caused by infections, cocaine or drugs ingestion that block sodium channels, which in turn allow to unmask the disease.

The hidden or intermittent form of the syndrome hinders timely diagnosis and increases the risk of sudden death (17). It is known that at rest or during sleep, a decrease in sympathetic activity can occur, which leads to an increase in the parasympathetic tone, increasing the possibility of suffering an arrhythmia that could lead to the death of the patient.

PERSPECTIVES AND RECOMMENDATIONS

Despite the research efforts made in Colombia, reports of patients with the disease are scarce; it is possible that one of the reasons for the limited records is related to the detection of BrS clinical manifestations, so that the syndrome goes unnoticed in most cases. Therefore, it would be important for specialists to instruct the medical staff in order to make a better diagnosis, to provide appropriate treatment to patients, and to avoid an increased risk of sudden death due to BrS.

In Colombia there are no reports on the expression of this syndrome during pregnancy, so it is suggested to carry out studies during this stage, in this way it would be possible to recognize the symptoms that appear in this period, and the role of hormones in the syndrome would be more understandable.
It is important to complement these studies with *in vivo* investigations using biomodels, which allow not only to better understand the mechanisms by which the syndrome acts, but also to propose more effective treatments for patients.

**CONFLICT OF INTEREST**

None to declare.
BIBLIOGRAPHIC REFERENCES


24. Chiale PA, Franco DA, Selva H, Militello CA. Supradesnivel persistente del segmento ST en las derivaciones precordiales derechas y muerte súbita por


